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MUSCULAR WASTING OF OBSCURE ORIGIN AND THE THYROID GLAND[1]

KENNETH L. ZIERLER

Departments of Medicine and Environmental Medicine, The Johns Hopkins University and Hospital

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Participation of skeletal muscle in the total response to overactivity of the thyroid gland has been recognized for more than half a century (1, 2). Although it is unlikely that muscle ever escapes entirely the effects of hyperthyroidism, those patients in whom involvement of muscle is the most striking feature have been subclassified as examples of thyrotoxic myopathy (18). By 1942 thirteen instances of chronic thyrotoxic myopathy had been reported and admirably summarized by McEachern and Ross who contributed three cases of their own (10). Noteworthy is the fact that 11 of these 13 patients were beyond the age of 40 years. Thorn and Eder added five cases in 1946 (21) of whom one, a 22 year old woman, appears to have been an example of exophthalmic goiter and not properly included in the group under discussion; the remainder were 40 years or older.

Many characteristics presented by patients with chronic thyrotoxic myopathy are reminiscent of those recounted by Lahey in his description of "apathetic thyroidism" (8). Although Lahey does not emphasize involvement of skeletal muscle, his patients tended to be over 40 or 50 years of age and had marked loss of weight. No unequivocal definition separates apathetic thyroidism from chronic thyrotoxic myopathy.

Despite accumulated reports, recognition of the thyroid factor in patients beyond the age of 40 presenting the spectrum of this disease continues to be difficult. For this reason, and because our experience differs in some details from that previously recorded, there is described here a specific group of cases of hyperthyroidism in patients past 40 years of age seen at the Johns Hopkins Hospital between 1946 and 1950.

CASE MATERIAL AND METHODS

Observations of 10 patients past 40 years of age are included in this report. The cases were selected only because they were seen by the same observer and because wasting of muscle was a prominent common denominator; it is not intended to review the total experience of this institution. Although in most cases corroborative evidence of hyperthyroidism was obtained, the diagnosis of hyperthyroidism was considered established finally by favorable response to specific antithyroid treatment. Objective measures of favorable response were multiple but the one considered most significant was an appreciable gain in body weight.

[1] Aided by a contract between the Office of Naval Research, Department of the Navy and The Johns Hopkins University (NR113-241).

In seven patients an estimate of creatine metabolism was performed. Creatine and creatinine determinations on serum and urine were performed by the method of Peters (13). In five patients creatine tolerance tests, employing 2.64 g. of creatine hydrate as the test dose, were carried out according to Thorn's procedure (19). In one patient the renal clearance of creatine was determined by a technique described previously (27).

Adrenocortical function was tested by one or more of three methods in six patients: the water diuresis test described by Robinson, Power, and Kepler (15), the salt deprivation test of Wilder (3), and the response of circulating eosinophiles to administered adrenocorticotrophic hormone (22).

TABLE 1

Early Manifestations of Illness

	INITIAL MANIFESTATIONS OF ILLNESS	COMPLAINTS AT TIME OF ADMISSION
Emotional lability	5	8
Weight loss	4	7
Weakness	1	7
Anorexia	2	5
Sweating	1	4
Palpitations	1	3
Tremors	1	3
Increased appetite	1	2
Nausea and vomiting	2	2
Dyspnea	1	2

At the time of admission the following complaints occurred once each: diarrhea, polydipsia and polyuria, exophthalmos, swelling of neck, dysphagia, intolerance to heat.

The digits refer to the number of patients who presented the corresponding complaint. Their total exceeds ten, the number of patients, because each patient had multiple complaints.

CLINICAL DESCRIPTION

The complex nature of the disease is illustrated by three examples reported in detail in the appendix.

Despite impressive exceptions a trend characteristic of most of the patients is discernible. In the composite, the patient was apt to be a male, over 50 years of age (Table 2), who described himself as having been well until two to nine months before seeking medical attention. However, interpretation of symptoms sometimes suggested that the illness may have existed for five years or more. Thus, two patients described episodes of tachycardia over a seven to ten year period. Under observation, similar episodes in these two patients proved to be paroxysmal auricular fibrillation. A third patient was aware of gradual loss of weight for five or six years preceding admission. In most instances the patient complained chiefly of loss of weight, either sudden or gradual, accompanied by weakness and anorexia (Table 1). Weight loss was severe, usually 30 to 50 pounds, representing about 25 per cent of body weight (Table 2). Emotional lability was usually present, but seldom pronounced and

frequently interpreted to be commensurate with understandable anxiety in an older man who finds himself wasting away. Nevertheless, in two patients awareness of disease began abruptly in emotionally tense situations. Four patients appeared to be depressed, one so seriously that it was at one time suspected incorrectly that anorexia nervosa was responsible for the chain of events leading to weakness and loss of weight. The sequence of events, weakness and weight loss antedating other thyrotoxic symptoms, described by Morgan and Williams (11), did not occur regularly in our patients.

On examination, the patient was afebrile, apt to have a pulse rate of 80 to 110 per minute, a respiratory rate of 20 to 30, and an arterial blood pressure which was normal or marked by slight elevation of systolic tension.

TABLE 2

Degree of Weight Loss

CASE NO.	AGE	SEX	POUNDS LOST	PER CENT LOSS OF BODY WEIGHT	DURATION IN MONTH
1	61	M	80	42	12
2	43	F	65	40	2
3	72	M	51	28	8
4	69	M	50	25	5
5	65	M	40	24	8
6	54	M	31	21	?
7	60	M	30	22	3
8	49	M	29	17	6
9	52	M	28	21	14
10	63	M	20	16	6

Per cent loss of body weight is referred to the weight of the patient before illness.

Emaciation was almost always striking. Wasting was generalized but especially notable in the temporal muscles, muscles of the shoulder girdle, and the small muscles of the hands. There were no instances of ophthalmoplegia. Strength was reduced. Deep tendon reflexes were apt to be sluggish, in contrast to earlier reports in which exaggerated responses were described. Since strength of response is related to muscle mass, it is not surprising that hypoactive reflexes occurred in hyperthyroid subjects in whom wasting was manifest. Sometimes the reflexes were normal or brisk; they were not always symmetrically so. Plantar response was almost always flexor, but one patient developed a persistent unequivocally extensor response while under observation. Muscle fasciculation was occasionally present, less often than in previously recorded cases. Sensation was intact.

The skin was loose, but usually fine, smooth and warm. In one patient discrete brown pigmentation over the chest and abdomen was sufficiently impressive to be considered consistent with Addison's disease. There was usually

tremor of the extended fingers and, less frequently, of the tongue. The patients sometimes appeared restless and anxious, but not consistently so.

The eyes were unremarkable, on the whole. In six patients the globes were not prominent; of the remaining four, although exophthalmometry indicated prominence, observers were seldom impressed. Weakness of convergence was noted twice; lid lag, only once. Ability to wrinkle the forehead was always present. Chemosis never occurred.

The thyroid was normal in size and consistency in eight of the ten patients. One patient had noticeable goiter. Thrill or bruit over the thyroid was almost always absent.

There tended to be neither enlargement or overactivity of the heart. Cardiac rhythm was usually regular; two patients had transient auricular fibrillation. Veins were not engorged. Minimal dependent edema was present in two patients.

Except for an occasional non-tender, non-pulsating, minimally enlarged liver the rest of the examination was usually normal.

Routine urinalysis revealed no abnormality. Transient glycosuria was noted only once. Hemoglobin was often deficient, 10 or 11 g. per 100 ml. Erythrocytes were normal or slightly reduced in number. The white blood count was normal, occasionally with a relative lymphocytosis. The erythrocyte sedimentation rate was apt to be accelerated.

In the light of this summary it is not surprising that the initial impression of physicians was carcinoma, probably intra-abdominal, in four of ten patients. In a fifth patient, in whom the diagnosis of hyperthyroidism was entertained originally, evidence was considered so unconvincing that a search for carcinoma was undertaken. Because the initial impression of physicians seeing these patients is descriptive of the diagnostic problem, they have been listed in Table 3.

Further investigation, not related primarily to the thyroid, was of value only in retrospect. Those studies that emphasize contrasts with or similarities to typical hyperthyroidism are cited below.

Relative freedom from serious *cardiovascular* disease was reflected in clinical measurement. Venous pressure was normal. Circulation time (arm to tongue), measured in three patients, was not accelerated. Electrocardiograms were studied in seven patients. High, peaked P waves were present in three, an occurrence reported in association with hyperthyroidism (7). One patient, case 2, E. A., in addition to high P waves, exhibited depressed T waves and a long QT interval concurrently with hypocalcemia and hypokalemia.

Laboratory evidence of slight impairment of *liver* function was obtained in many patients (Table 4). The incidence of impaired excretory function may have been greater than seen ordinarily in typical hyperthyroidism. This fact

might have been predicted from the early experience of Yeomans and Warfield (25) who found that among 44 hyperthyroid patients, of those above 40, two-

TABLE 3

Tentative Diagnoses Made in Patients with Hyperthyroidism

DIAGNOSIS	NUMBER OF TIMES MADE	NUMBER OF PATIENTS
Hyperthyroidism	8	5
Carcinoma, probably intra-abdominal	5	4
Arteriosclerotic heart disease	2	2
Addison's disease	2	2
Diabetes insipidus	2	1
Primary emotional disturbance	2	2
Progressive muscular atrophy	1	1
Amyotrophic lateral sclerosis	1	1
Destructive intracranial lesion	1	1

The purpose of this table is emphasis, not that physicians can err, but that in half the patients manifestations of disease were so bizarre that hyperthyroidism was not even considered. Although there were but 10 patients, the total observations in each of the two columns of figures exceeds 10 because most patients were seen by more than one physician.

TABLE 4

Liver Function

CASE NO.	ICTERUS INDEX	SERUM BILIRUBIN		BSP	CEPHALIN FLOC.	THYMOL TURBIDITY	ALKALINE PHOSPHATASE	SERUM	
		Total	Direct					Albumin	Globulin
1. H. C.	10.0	1.2	1.1	2.4	0	3.2	10.0	4.2	3.7
2. E. A.	10.0	2.2	0.9	1.2	0	1.3	7.8	2.0	2.6
3. D. G.	8.0	2.5	0.9	0.6			5.9	6.0*	
4. E. B.	4.0	1.0	0.8				4.4	4.3	2.5
5. W. F. S.	7.0			1.8	+	7.8	4.9	4.0	2.7
8. H. P.	7.0			1.1				7.0*	
9. W. A.	7.5	1.8	1.1	1.7	0	1.4		3.9	3.2
10. J. F.	<7.0	<0.8				2.4	10.9	4.7	2.7

* Total protein by refractive index.

BSP indicates retention of bromsulphalein, mg. per 100 ml. of serum, 30 minutes after intravenous injection of 5 mg. per k. body weight of the dye. Alkaline phosphatase is expressed in Bodansky units.

thirds had reduced hepatic function; of those below 40, less than one-third had hepatic impairment as measured by the phenoltetrachlorphthalein test.

Disturbance of *renal function* was manifest in only one patient, case 2, E. A., who presented a diabetes insipidus-like state. The mechanism of this defect is considered further in the abstract of this patient's record.

Neuromuscular studies were confined to testing with neostigmine and to investigation of creatine metabolism. In three patients examined, no improve-

ment in strength followed administration of neostigmine. Observations on creatine metabolism are reported in a later section.

Carbohydrate metabolism, in contrast to the usual findings in younger patients with hyperthyroidism (4), was almost always normal. Spontaneous glycosuria was not observed in nine of the ten patients. The tenth patient had 2 plus glycosuria at the time of his first visit to the outpatient department; ten subsequent urinalyses failed to reveal the presence of sugar. In seven of eight patients blood glucose concentration in the fasting state was invariably normal. Glucose tolerance tests, performed on four patients, were normal in three. A diabetic response occurred in the fourth patient.

ESTABLISHMENT OF DIAGNOSIS

In four instances the combination of weight loss, tachycardia, and emotional lability was sufficiently impressive to make hyperthyroidism the most likely diagnosis from the start. In the remaining cases continued observation turned suspicion toward the thyroid. In all ten patients repeated determinations demonstrated elevated basal metabolic rates. Diagnosis was aided in one case by determination of the concentration of protein-bound iodine in serum, and in another case by measurement of the rate of radioiodine uptake. In both instances the results are abnormally high, consistent with hyperthyroidism.

Creatine tolerance tests were performed in five patients. The pattern of creatine and creatinine excretion was uniform and relatively unique; these patients exhibited hypocreatininuria in the absence of commensurate spontaneous creatinuria. Once this combination was noted its appearance in subsequent cases served to intensify the search for hyperthyroidism. Further consideration of creatine metabolism in this disease is reserved for a later section.

In the final analysis, diagnosis depended almost always on the results of therapy directed toward amelioration of hyperthyroidism. Whether treatment consisted of administration of Lugol's solution (strong solution of iodine) or of *n*-propyl thiouracil or of both, the response was rapid (Figure 1). All patients began to gain weight quickly, as much as 10 to 30 pounds during the first month. Within two months to a year they had returned to their normal weight (Table 5). Simultaneously, there was renewal of strength and of well-being. Those patients who had been anoretic enjoyed return of appetite. Basal metabolic rate fell to normal and the concentration of cholesterol in serum rose, even in those patients in whom it had appeared to be normal during the height of disease. The consistency of increase in cholesterol concentration in response to therapy as opposed to the fact that "low" cholesterol concentrations did not appear regularly in untreated cases is probably a reflection of the fact that in older patients limits of "normal" serum cholesterol concentrations must be scaled upward.

Rapid restitution of health in these patients is especially gratifying when one recalls the high mortality rate in unrecognized or undertreated cases. Thus, Morgan and Williams had one death in four cases (11); McEachern and Ross, one in three (10); Thorn and Eder, one in four (21). Death is reported to be related to feebleness of muscles of respiration, involvement of which, incidentally, may be the explanation, in part, of dyspnea and tachypnea observed in half of our patients.

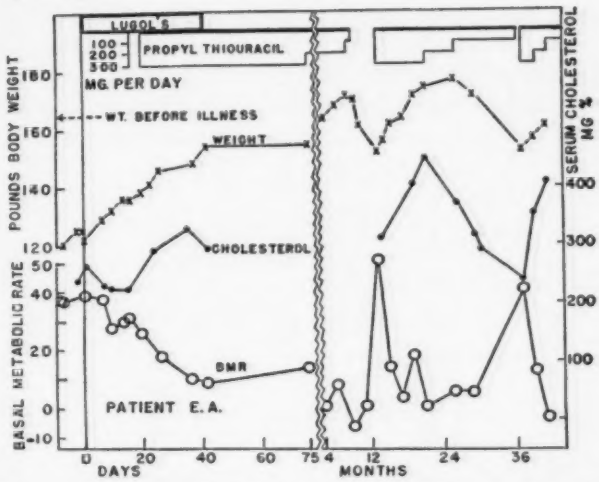

FIG. 1. Response of case 2, patient E. A., to antithyroid therapy. Note parallel changes in body weight and in serum cholesterol concentration and reciprocal changes in basal metabolic rate. The dependence of these parameters upon the dose of *n*-propyl thiouracil is illustrated by the fall in weight and in cholesterol concentration accompanying reduction of and discontinuance of therapy and the prompt response to resumption of treatment. Usefulness of serial determination of cholesterol concentration is demonstrated by alterations that occur despite an apparently "normal" concentration during the disease.

CREATINE METABOLISM

A. Excretion of creatine

Creatine, synthesized in the liver, is concentrated a thousand-fold in skeletal muscle and excreted slightly or not at all in the urine of normal adults. In certain pathological states creatinuria occurs. Among the first so described were cases of exophthalmic goiter (16), and many subsequent studies have confirmed that spontaneous creatinuria is a regular feature in this sort of hyperthyroidism. For example, in 31 patients with exophthalmic goiter, Palmer et al. found creatinuria in all (12). Twenty-nine of these excreted more than 100 mg. and fifteen excreted more than 500 mg. of creatine a day.

Since there is a renal threshold for creatine (23), its excretion in the urine

TABLE 5

Response to Treatment

CASE NO.	WEIGHT DURING HEALTH	BEFORE TREATMENT			DURING TREATMENT						MONTHS TAKEN TO REGAIN NORMAL WEIGHT
					After One Month			After Two Months			
		Wt.	BMR	Cholesterol	Wt.	BMR	Cholesterol	Wt.	BMR	Cholesterol	
1. H. C.	195	110	+39	89	120	+13	158	136	−10	181	?
2. E. A.	165	121	+33 to +47	200 to 264	149	+10	329	155	+14	309	4
3. D G.	165	108	+57 to +74	163	130	+33	235	—	—	—	—
4. E. B.	200	147	+19 to +41	203	163*	+2*	258*	—	—	—	—
5. W. F. S.	170	129	+39 to +45	182	135†	+20†	—	158‡	+12‡	—	6
6. C. H.	150	113	+28 to +65	137	128	—	—	134‡	+18‡	200‡	12
7. W. S.	145	109	+41	137	117	+24	—	123	+4	—	—
8. H. P.	173	140	+36 to +45	175	146†	+23†	220†	169	+6	315	3
9. W. A.	135	89	+73 to +86	226	103	+48	258	128§	+27§	395§	11
10. J. F.	130	109	+51 to +60	188	119	+25	227	130‡	+33‡	178‡	3

* After 6 weeks of treatment
† After 2 weeks of treatment
‡ After 3 months of treatment
§ After 5 months of treatment
? Developed myxedema
Patient E. B. had a perforated tympanic membrane; BMR's are unreliable.

can result only if its concentration in plasma exceeds the normal threshold or if the renal threshold is lowered or both. It has been shown that in typical hyperthryoidism the concentration of creatine in plasma is elevated beyond the normal renal threshold (23) and renal tubular mechanisms operate with normal efficiency (26). Therefore, creatinuria in exophthalmic goiter is the result of pre-renal disturbance, the nature of which has not been established. However, it is essential to note that simple reduction in muscle mass is an adequate cause of creatinuria provided normal velocity of synthesis of creatine is maintained and renal threshold is not elevated (26).

As we have seen, wasting of muscle is a hall-mark of hyperthyroidism in older patients. If creatinuria occurs in typical hyperthyroidism, one would expect to find it exaggerated in these cases. It is surprising, therefore, to note

TABLE 6

Creatine Metabolism

CASE NO.	MG. EXCRETED PER 24 HOURS		CREATINE TOLERANCE PER CENT	CREATININE COEFFICIENT
	Creatinine	Creatine		
1	470	109	65	9.4
2	355	0	49	6.4
3	680	9	<77	13.7
4	708	0		10.6
5	930	40	44	15.8
8	1177	0		18.5
10	838	10	<50	16.9
Normal Male.....		<60	>80	>20

the absence of significant creatinuria in most of our patients and in none of them was creatinuria commensurate with the degree of muscle atrophy. Of seven patients studied, three had no creatinuria, three more excreted 40 or less mg. a day, and one excreted 109 mg. a day (Table 6). It is not unusual to find as much as 60 mg. of creatine in the daily urine of normal males beyond the age of 50.

B. Excretion of creatinine

Evidence is excellent for the thesis that the sole virtual source of urinary creatinine is creatine or phosphocreatine. Since some 95 per cent of body creatine is located in skeletal muscle, its conversion to creatinine is largely a function of muscle. In health, urinary excretion of creatinine is relatively constant and proportional to body weight. When muscle is lost from the body, excretion of creatinine is reduced proportionately. So reliable is this relationship that it has been suggested that the degree of reduction in the creatinine coefficient (mg. creatinine excreted per day per kg. body weight) is a quantita-

tive measure of remaining muscle mass (17). It is not unexpected, therefore, to note that the seven older hyperthyroids included in this study all had hypocreatininuria and reduction in the creatinine index (Table 6). One patient was followed during recovery; her creatinine index doubled one month after institution of therapy with Lugol's solution, coincident with 50 per cent increase in her body weight.

C. Creatine tolerance

Richardson and Shorr (14) were the first to show that measurement of creatinuria induced by a standard load of creatine was a useful test in hyperthyroidism. Thorn (19) modified the test by doubling the creatine load. Normal males retain 80 to 100 per cent of the dose of creatine administered in the latter test. Retention less than this suggests defective renal tubular reabsorption or pathological elevation of the concentration of creatine in circulating plasma. The latter may occur as a result of inadequate disposition of creatine to skeletal muscle either owing to loss of muscle tissue or to failure of the mechanism responsible for transfer to creatine across the muscle cell membrane. Impaired creatine tolerance is to be expected, therefore, wherever there is extensive atrophy of muscle. It is found commonly in typical hyperthyroidism (19).

Creatine tolerance tests were performed in five older hyperthyroid patients; impaired tolerance uniformly occurred (Table 6). When the test was repeated in one patient during the course of antithyroid treatment, her tolerance doubled coincidentally with doubling of her creatinine index and 50 per cent increase in her body weight.

DISCUSSION

Among the questions called to mind by the present group of patients, two may be considered further.

The first question is concerned with the subordination of several customary signs of hyperthyroidism in patients with thyrotoxic myopathy. Since this form of the disease tends to occur in older patients, the process of aging may modify in some way the response to hyperthyroidism. Alteration in function with aging is not infrequently associated with endocrine or with intrinsic vascular changes. It may be profitable, therefore, to speculate upon the role of another endocrine gland in the production of the symptoms of hyperthyroidism.

A brief survey of manifestations regarded commonly as typical of hyperthyroidism suggests that many are related to adrenomedullary-like activity. These include palpitations, tachycardia, systolic hypertension, sweating, and perhaps the anxiety state and disturbances of carbohydrate metabolism. Exquisite sensitivity of patients with typical hyperthyroidism to administered epinephrine is well known (5), and it is possible that at least part of the phe-

nomena exhibited by hyperthyroid subjects are in consequence of over-reaction to endogenous epinephrine.

If this is so, the apathetic aspect of older hyperthyroids may be the result of lack of sensitivity to epinephrine or to decrease in the production of endogenous epinephrine.

Although it would be of interest to study sensitivity to epinephrine in older hyperthyroids, such an investigation is not without hazard and was, therefore, not pursued. However, epinephrine was administered to one such patient, not included in the reported group. The patient, a 55-year old housewife, seen at another hospital in 1941, was characteristic of the group under consideration. She was weak and emaciated, and, despite a small nodular goiter, it was suspected that she might have carcinoma of the gastrointestinal tract. During investigation of this possibility gastric analysis was performed. Within two minutes after subcutaneous exhibition of 0.5 mg. of histamine the patient became flushed and faint. To modify the histamine reaction she was given, subcutaneously, 0.5 ml. of 1:1000 epinephrine. In 10 minutes she had marked pressor and cardio-accelerator response with dramatic emotional concomitants. Her pulse rate, usually 80 to 90, rose to 140 and her arterial tension, usually 125/65, rose to 190/100. Subsequent investigation demonstrated the presence of hyperthyroidism, and the patient responded to administration of Lugol's solution and to subtotal thyroidectomy.

It is suggested, therefore, as frank speculation, that the apathetic aspect of these hyperthyroids may be owing in part to diminution in secretion of adrenomedullary hormones despite the fact that the capacity to react with exaggeration to administered epinephrine may be comparable to that of patients with typical hyperthyroidism.

The second question is concerned with the apparently anomalous pattern of creatine metabolism.

Given the constellation of weight loss, muscle atrophy, hypocreatininuria, and accelerated excretion of exogenous creatine (impaired creatine tolerance), an explanation must be sought for the failure to excrete expected quantities of endogeneous creatine. A similar array is seen in patients with myotonic dystrophy who also fail to exhibit spontaneous creatinuria commensurate with the degree of muscle wasting (26). These findings were reminiscent of those we had noted in a patient with Addison's disease. Indeed, absence of creatinuria in Addison's disease was noted with surprise more than 40 years ago (24). More recent study has confirmed that, while creatinuria is not always lacking in Addison's disease, it is seldom as great as anticipated in view of the loss of muscle and the reduction in excretion of creatinine (6). Nevertheless, in Addison's disease, creatine tolerance usually is impaired (20). Although direct evidence is not available, this apparently anomalous behavior of creatine is

consistent with the hypothesis that the velocity of creatine synthesis is retarded in these diseases.

Despite the resemblance of the pattern of creatine metabolism to that seen in Addison's disease, no evidence of adrenocortical dysfunction was found in this group of hyperthyroid patients. Thus, in two patients response to the Wilder test was normal, in one patient urinary excretion of 11-oxysteroids was elevated, and in another patient there was eosinopenia. Although response to the Robinson-Power-Kepler test was positive in the five patients so studied, the test is not reliable in emaciated states (9).

SUMMARY

A group of ten patients beyond the age of 40 years was observed in whom hyperthyroidism was characterized mainly by great wasting of muscle. These patients complained chiefly of anorexia, weakness, and weight loss. Exophthalmos, thyropathic eye signs, and goiter were not demonstrable or were not impressive in most cases. However, other symptoms and signs associated with typical hyperthyroidism in younger patients were almost always present, though seldom prominent and sometimes overlooked.

A curious pattern of creatine metabolism appeared in these patients, characterized by hypocreatininuria, impaired creatine tolerance, and surprisingly trivial spontaneous creatinuria. So consistent was this pattern that it became a useful indication for therapeutic trial. The pattern is known not to be specific; it occurs in myotonic dystrophy and in Addison's disease. However, efforts to demonstrate adrenocortical insufficiency in older hyperthyroids were unsuccessful. The observations may be explained by assuming that the velocity of synthesis of creatine is depressed in the three clinical states in which this anomalous creatine pattern has been noted.

In the final analysis, convincing demonstration of hyperthyroidism depended upon response to therapy. Rapid recovery of weight and restoration of strength occurred uniformly during administration of Lugol's solution or of *n*-propyl thiouracil or of both.

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APPENDIX

ILLUSTRATIVE CASES

Case 2. E. A., Unit No. 410290, 43-year old housewife, was admitted to the hospital on January 18, 1947, complaining chiefly of abdominal discomfort and vomiting of two months duration. One year prior to admission she had noticed a small nodule in her neck. During the summer of 1946 she became aware of increasing fatigability and weakness, and in July menopause occurred. At about this time she noted loss of axillary and pubic hair. In November she began to have ill-defined epigastric discomfort followed by anorexia and profuse watery diarrhea. Shortly thereafter, and until admission, she vomited almost daily on arising. Diarrhea, however, persisted for only a week or so, but recurred in brief bouts thereafter. Weight loss was rapid and severe, amounting to 65 pounds by the time of admission. Insidiously, during the two-month period she developed excessive thirst and she urinated almost hourly day and night.

Examination revealed an emaciated woman, appearing chronically ill. Temperature was 98°; pulse rate, 112 per minute, respiratory rate, 22 per minute; blood pressure. 110 mm. Hg systolic, 75 diastolic; weight, 100 pounds. There was moderate generalized edema involving all four extremities, sacral area, and abdominal wall. Axillary and pubic hair were almost completely absent. Eyes were normally prominent and there were no thyropathic eye signs. There was cheilosis on the right. Teeth were extremely carious. The tongue was red with partial papillary atrophy along its margins. A small nodule was palpable in the region of the thyroid isthmus, although not all observers agreed upon this observation. There was no thrill or bruit over the thyroid. Cervical veins were not engorged. Lungs were clear. The precordium was quiet. The heart was not enlarged. Rhythm was regular. There were no murmurs. Venous pressure was equivalent to 68 mm. of water. Circulation time (decholin) was 18 seconds. There was minimal ascites. Liver edge was just palpable. There was marked generalized wasting. Temporal fossae were excavated. The sternomastoids, biceps and triceps were virtual strings. Trapezii and pectoralis muscles were so thin that bony landmarks showed clearly from beneath. Gluteal atrophy was extreme. Motor power was greatly reduced; she could not raise her legs from the bed. Grip was feeble. She had the appearance of left facial weakness. Deep tendon reflexes were hypoactive, but were slightly more brisk on the left. There was an equivocal left plantar response on admission; by February 8 the left plantar response was definitely extensor. There were no tremors and no fasciculation. Sensation was intact.

Serological test for syphilis was negative. Hemoglobin was 12.5 g. per cent. Red blood count was 4.83 million per cu.mm. Hematocrit was 40 per cent. White blood count was 17,600 per cu.mm. on admission, with 90 per cent segmented neutrophiles. Subsequent white blood counts varied between 7,200 and 9,400 with normal distribution. Erythrocyte sedimentation rate was 22 mm. per hour, corrected. Icterus index was 10.

Specific gravity of the urine was 1.000 to 1.001 and it could not be increased by administration of pitressin. Urine pH was 6.0. Urine contained no sugar, a trace of protein, no formed elements. Sulkowitch test was negative. On admission she excreted in 15 minutes none, and in two hours 55 per cent of a test dose of phenolsulfonphthalein despite excellent diuresis. Urea clearance was 55 per cent of normal.

Chemical analysis of blood on admission gave the following results: non-protein nitrogen, 29 mg. per cent; fasting blood sugar, 172 mg. per cent (although three subsequent determinations prior to specific antithyroid therapy gave concentrations varying from 76 to 88 mg. per cent); chloride, 102.5 mEq. per liter; carbon dioxide combining power, 27.9 mEq. per liter; sodium, 146 mEq. per liter; potassium, 2 mEq. per liter; cholesterol, 200 mg. per cent;

calcium, 4.6 mg. per cent; phosphate, 1.7 mg. per cent; alkaline phosphatase, 7.8 units; bilirubin, 2.2 mg. per cent total, 0.9 mg. per cent direct; albumin, 2.0 g. per cent; globulin, 2.6 g. per cent.

An oral glucose tolerance test was not remarkable in the light of her starvation diet. Insulin tolerance was normal.

Lumbar puncture revealed no abnormalities.

She was offered a high caloric diet with fluids ad libitum. During the first three hospital days she consumed between 6500 and 9000 ml. of fluid per day. Her urine output varied from 4000 to 5600 ml. per day. It was suspected that she had diabetes insipidus, possibly associated with a destructive basilar lesion. However, she did not respond to pitressin, five pressor units daily for six weeks.

On February 21, a course of vitamin D, 100,000 units a day, was begun. Although the calcium and phosphate concentration in her serum had been rising slowly since admission, the respective concentrations were still but 5.8 and 2.6 mg. per cent. At the end of six days of vitamin D therapy these values had become normal and remained so for the duration of her hospitalization.

Despite slight improvement in nutrition the patient remained seriously ill. Assay of 24-hour excretion of follicle-stimulating hormone was positive to 96 mouse units, negative to 192 mouse units, probably incompatible with a destructive lesion of the anterior pituitary.

Basal metabolic rates had been determined early in her course; they were +47 and +33 per cent of normal. However, these results were ignored as inconsistent with the clinical syndrome. On February 24 creatine metabolism was studied. The patient had hypocreatininuria without creatinuria, and her creatine tolerance was only 49 per cent. This observation stimulated further search for hyperthyroidism. Three subsequent determinations of basal metabolic rate were +38, +37, and +39 per cent of normal. The concentration of protein-bound iodine in her serum was 12.5 μg. per 100 ml. (normal, 4 to 8 μg.).* On March 19 she began a course of Lugol's solution, 3 ml. per day. Although steady increase in weight followed administration of this drug, the drop in metabolic rate was not swift. On April 6 *n*-propyl thiouracil, 300 mg. per day was added. Response was more rapid. The patient's course is illustrated in Figure 1.

By the time she was discharged from the hospital on April 29, 1947 she had improved dramatically. Muscle bulk had returned and her strength was normal. The apparent facial palsy had disappeared and, in retrospect, must have been the result of asymmetric intrinsic weakness of facial muscles. She had no abdominal complaints. Edema had disappeared. Her urine output had dropped to one to three liters per day, and she was able to concentrate her urine to a specific gravity of 1.020. Excretion of phenolsulfonphthalein had risen to 20 per cent in 15 minutes, and to 70 per cent in two hours. Serum electrolyte abnormalities had been corrected; sodium concentration had dropped to 138 mEq. per liter; potassium had risen to 4.2 mEq. per liter. Serum albumin had increased to 4.1 g. per cent; globulin to 3.5 g. per cent.

She continued to take *n*-propyl thiouracil at home, but Lugol's solution was discontinued. Beginning June 2, 1947 the dose of *n*-propyl thiouracil was reduced and on December 18 the drug was discontinued. By April 14, 1948 relapse was obvious. She had lost 20 pounds from her maximum weight and complained of weakness and nervousness. Treatment with *n*-propyl thiouracil was re-instituted and response was rapid. On April 1, 1950 the patient abandoned therapy. In less than two weeks she noted nervousness, palpitations and insomnia. Again she had lost 20 pounds. Treatment was resumed and response was rapid once

* We are indebted to Dr. William T. Salter for the determination of protein-bound iodine.

more. She appears, after three years, to require a maintenance dose of about 100 mg. of *n*-propyl thiouracil per day.

Case 4. E. B., Unit No. 545938, 69-year old retired executive, was admitted July 31, 1950, complaining of weight loss of five months duration.† He had always been in excellent health until March 28, 1950 when he had an acute illness manifested by malaise and cough productive of thick brownish sputum. Although he recovered from the acute disease he did not regain health. He became increasingly nervous; he lost weight, was anoretic, and became progressively weaker. On April 1 he had weighed 200 pounds. By the time of admission, five months later, he weighed only 153 pounds. Despite his history of good health, records of his annual physical examination indicated that for about five years preceding admission he had had a pulse rate of approximately 100 per minute.

Examination revealed a tall, gaunt man in no evident distress. Temperature was 98.8°; pulse rate, 110 per minute; respiratory rate, 15 per minute; blood pressure 155 mm. Hg systolic, 100 diastolic. There was evidence of marked weight loss. Over the hypochondrium there was mottled brownish pigmentation. The eyes were not prominent. There were no thyropathic eye signs. Mucous membranes were not pigmented. Thyroid was barely palpable and there was no thrill or bruit. Lungs were clear. Heart was not enlarged. Rhythm was totally irregular. Abdomen was unremarkable. Wasting was generalized and symmetrical.

The pectoral and quadriceps muscles suffered the greatest degree of atrophy. Moderate atrophy was obvious in the sternomastoids, deltoids, biceps, triceps, interossei, muscles of the thenar and hypothenar eminences, the hamstrings, the gastrocnemii, and the peroneals. Weakness was general but spared the facial muscles. No abnormal fatigue was elicited. There was no myotonia. Occasional fasciculations, especially about the trapezius, were seen by one observer but not by others. Deep tendon reflexes were sluggish. Cremasteric response was absent. The left plantar response was equivocal to extensor. There was no clonus. Sensation was intact.

Serological test for syphilis was negative. He had no anemia. White blood count was 5200 per cu. mm. with 48 per cent segmented neutrophiles, 37 per cent lymphocytes, 10 per cent monocytes. Erythrocyte sedimentation rate was 22 mm. per hour, corrected. Urine was unremarkable. Chemical examination of blood revealed the following concentrations: nonprotein nitrogen, 33 mg. per cent; fasting blood sugar, 84 mg. per cent; cholesterol, 203 mg. per cent; albumin, 4.3 g. per cent; globulin, 2.5 g. per cent; phosphorus, 4.2 mg. per cent; alkaline phosphatase, 4.4 Bodansky units; bilirubin, 1.0 mg. per cent total, 0.8 mg. per cent direct; sodium, 138.2 mEq. per liter; potassium, 4.3 mEq. per liter; chloride, 107.1 mEq. per liter; carbon dioxide combining power, 25 mEq. per liter.

It was suspected by some observers that the patient had Addison's disease or an intra-abdominal neoplasm. Other observers suspected progressive muscular atrophy or amyotrophic lateral sclerosis. Roentgenographic survey failed to reveal evidence of gastrointestinal neoplasm. The Robinson-Power-Kepler test, parts I and II, were positive. However, response to the Wilder test was normal. His blood eosinophile concentration was low, 22 per cu. mm. on the day of admission and 11 per cu. mm. on the morning of the test day, so that the response to administration of adrenocorticotropic hormone cannot be evaluated with assurance. The eosinophiles, four hours after administration of 25 mg. of ACTH were 5 per cu. mm. Thus, no substantial evidence of adrenal insufficiency was obtained.

Basal metabolic rates were determined on two occasions; they were +41 and +19 per cent of normal. The patient had hypocreatininuria but no creatinuria. Uptake by the thyroid

† I am indebted to Dr. Palmer Futcher, whose patient this was, for the opportunity of observing the patient.

gland of a tracer dose of radioiodine was accelerated.‡ On August 22 treatment started: Lugol's solution 1.5 ml. per day and *n*-propyl thiouracil 300 mg. per day. By that time his weight had fallen to 147 pounds. Basal metabolic rate the next morning was +1 per cent of normal; however, it was discovered that the patient had a perforated tympanic membrane and no reliability could be assigned these determinations. On October 3, after six weeks of therapy he weighed 163 pounds, a gain of 16 pounds. His appetite was restored. He was stronger, although he still tired easily. The plantar extensor response had disappeared. Abdominal pigmentation had faded in part.

Case 10. J. F., Unit No. 387765, 63-year old retired restaurant operator, was admitted to the hospital July 12, 1946, complaining chiefly of nervousness of six months duration. His illness seemed to begin a year before admission, at which time there was the onset of urinary hesitancy, dribbling and nocturia. Sleep was poor and he was anoretic. He was disturbed by muscle twitching and by excessive sweating. He had nocturnal palpitation and moderate ankle edema, but no dyspnea. His appetite became worse, he had vague indigestion and he complained of constipation. In six months his weight fell from 130 to 110 pounds. In June, 1946 he appeared in the outpatient department where search failed to reveal disease of the gastrointestinal tract. To one observer his eyes seemed prominent and a basal metabolic rate was +67 per cent of normal. The patient was admitted to the hospital for investigation.

On admission he appeared chronically ill, depressed, and had evident weight loss. There was no edema. His temperature was 98.6°; pulse rate, 76 per minute; respiratory rate, 18 per minute; blood pressure, 130 mm. Hg systolic, 60 diastolic. His eyes were completely unremarkable. The thyroid was just palpable; there was no thrill or bruit over it. There was slight tremor of the extended tongue and hands. Scattered rhonchi were heard at both lung bases. The heart was not enlarged. Rhythm was regular. The first mitral sound was accentuated and there was a loud apical systolic murmur. Veins were not engorged. Venous pressure was equivalent to 55 mm. of water. The abdomen was unremarkable. The prostate was slightly enlarged and firm. Muscle wasting was generalized, but most obvious in the temporal area, the small muscles of the hand and the pectoral and pelvic girdles. Weakness was proportional to wasting; facial muscles were spared. Deep tendon reflexes were sluggish. Plantar response was flexor. There was no fasciculation. Sensation was intact.

There was slight anemia; hematocrit was 34.5 per cent; hemoglobin, 10.2 g. per cent; red blood cells, 3.79 million per cu. mm. There were 7,000 white blood cells per cu. mm. with a normal differential count. Erythrocyte sedimentation rate was 25 mm. per hour, corrected. Urine was not abnormal except for a single instance of proteinuria associated with the appearance of occasional leucocytes.

Chemical analysis of blood revealed the following concentrations: non-protein nitrogen, 32 mg. per cent; fasting blood sugar, 88 mg. per cent; cholesterol, 175 mg. per cent; calcium, 10.1 mg. per cent; phosphate, 4.0 mg. per cent; alkaline phosphatase, 10.9 units; acid phosphatase, 2.9 units; albumin, 4.75 g. per cent; globulin, 2.74 g. per cent.

It was suspected that he had carcinomatosis, with the prostate as the possible primary site. However, the impression of the consulting urologist was that the patient had benign prostatic hypertrophy and roentgenographic survey revealed no evidence of metastases to bone. Repeated examination of the gastrointestinal tract again failed to disclose a primary tumor. During the course of gastric analysis, after administration of histamine, there was sudden onset of auricular fibrillation. When the arrhythmia persisted for 24 hours, quinidine, 0.2 g., was administered. Reversion to normal rhythm followed four hours later.

The patient excreted little or no creatine despite hypocreatinuria and impaired creatine

‡ Dr. Samuel Asper very kindly carried out the radioiodine study.

tolerance. It was suspected that he might have Addison's disease. The concentratons of sodium and of potassium in serum were normal. The Robinson-Power-Kepler test was positive, but the Wilder test was not consistent with adrenal insufficiency.

Finally, because four determinations of basal metabolic rate were elevated, +52 to +60 per cent of normal, therapeutic trial was begun on August 10. For fourteen months the patient received only Lugol's solution, 1.5 ml. per day. Within three months he had regained his usual weight, but there were fluctuations in his course thereafter. For this reason, *n*-propyl thiouracil, 300 mg. a day, was added in November, 1947. By May, 1948 he had regained his weight and his basal metabolic rate was −14 per cent of normal. When the dose of *n*-propyl thiouracil was reduced to 150 mg. a day the patient lost weight, 13 lbs. in four months, in association with increased oxygen consumption. Resumption of the larger dose of *n*-propyl thiouracil was followed by restoration of weight and reduction in metabolic rate. Although therapeutic management was difficult and certain facets of his illness appear to remain unexplained, response to antithyroid therapy over a period of three years is the basis for the assumption that the major illness was hyperthyroidism.

A VECTORCARDIOGRAPHIC STUDY OF THE "Q3" DEFLECTION IN CASES OF MYOCARDIAL INFARCTION AND IN NORMAL SUBJECTS*

W. R. MILNOR†, A. GENECIN, S. A. TALBOT, AND E. V. NEWMAN

WITH THE TECHNICAL ASSISTANCE OF J. T. HARPER

Department of Medicine, The Johns Hopkins University School of Medicine

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Although the appearance of "Q" waves in certain leads of the electrocardiogram characteristically accompanies myocardial infarction and necrosis, it is often difficult to distinguish such Q waves from those seen in persons without heart disease. The Q waves which develop after infarction often persist for years after the acute episode, and may constitute the only sign that infarction has occurred in the past, so that their recognition is of some practical importance. The differentiation of normal from abnormal Q waves in lead III is particularly difficult, and diagnostic criteria (2, 4), based on the duration and magnitude of the Q wave, the Q/R ratio, or the presence and characteristics of Q waves in other leads of the electrocardiogram are not always reliable (3).

One objective of our studies in vectorcardiography has been to see whether the spatial vectorcardiogram (1, 5), with its three-dimensional synthesis of the cardiac electrical field, might solve just such problems in clinical electrocardiography. This seems possible because electrical forces which look very similar in their projection on the frontal plane may actually be quite different when considered three-dimensionally. If the standard and unipolar extremity leads are assumed to lie in a single frontal plane, then two persons can show identical deflections in these leads, yet have very different spatial vectorcardiograms. One might expect the modifications of the cardiac electrical field caused by necrosis and scarring of the myocardium to differ considerably from the normal pattern, even though this might not be apparent in the frontal plane, and it seemed worthwhile therefore to examine the spatial vectorcardiograms in normal subjects and in those who had myocardial infarction and showed Q3 deflections in the ECG.

Vectorcardiograms were recorded from leads based on the Wilson "tetrahedron," (6), using lead I for the horizontal, lead VF for the vertical, and VB for the antero-posterior axes of our spacial reference system. The Wilson "central terminal," with connections to each arm and to the left leg through 5000 ohm resistors, was used. The posterior electrode for lead VB was placed

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† U. S. Public Health Service Research Fellow, National Heart Institute.

on the back just left of the midline, at the level of the 7th thoracic vertebra. The recording system was standardized so that 1.0 millivolt produced a deflection on the face of the cathode-ray tube of 1.0″ in leads I and VB, and 1.7″ in lead VF. Amplification could be increased or decreased stepwise after standardization. The standardization factor for the anterior-posterior lead was selected purely for convenience, instead of using the equally arbitrary isosceles or equilateral tetrahedron system. In our records the direction of electrical positivity is downward and to the observer's right, for all projections of the spatial vectorcardiogram. The sagittal projection is illustrated as if seen from the patient's right side.

Our vectorcardiograph includes a three-channel amplifier with a linear response from 0 to 150 c.p.s., and a time constant of 2.7 seconds. Frontal, sagittal, or transverse plane vectorcardiograms are displayed on a cathode-ray oscilloscope, and are photographed on 70 mm. film or paper, using a manual release to open and close the camera shutter. A more detailed discussion of vectorcardiographic technique and apparatus will be given in a subsequent paper.

The present report concerns 22 patients seen in the wards and outpatient departments of the Johns Hopkins Hospital, and in the Ritchie State Hospital. In each case there was good evidence that acute myocardial infarction had occurred previously, and all showed Q3 deflections in the electrocardiogram. The time of the acute episode varied from 6 days to 7 years prior to this study. Seventeen of this group were males and five females, and they varied in age from 36 to 75 years. Some were ambulatory and free of symptoms, while others suffered from angina pectoris, recurrent congestive failure, or moderate hypertension.

The control group consists of 31 persons from 18 to 62 years of age, with no evidence of heart disease or of other disease known to affect the electrocardiogram. Sixteen were males and fifteen females. Most of these subjects were members of the hospital staff, while the remainder were hospital patients with nothing in their clinical findings or past history to suggest cardiac disease. It is possible, of course, that some of this latter group may have had "silent" or unrecognized myocardial infarction in the past. An additional group of 14 persons whose electrocardiograms showed a Q3 were studied, but were excluded from this report because the available evidence for or against myocardial infarction was inconclusive.

Figure 1 shows a record typical of those in the normal group. Frontal and sagittal plane projections of the spatial vectorcardiogram are shown, and should be regarded as two views of a three-dimensional representation of one complete cardiac cycle, including the P, QRS and T "loops." The spatial QRS loop begins with a movement upward, forward, and a little toward the patient's left; it then changes direction rather abruptly, and moves downward,

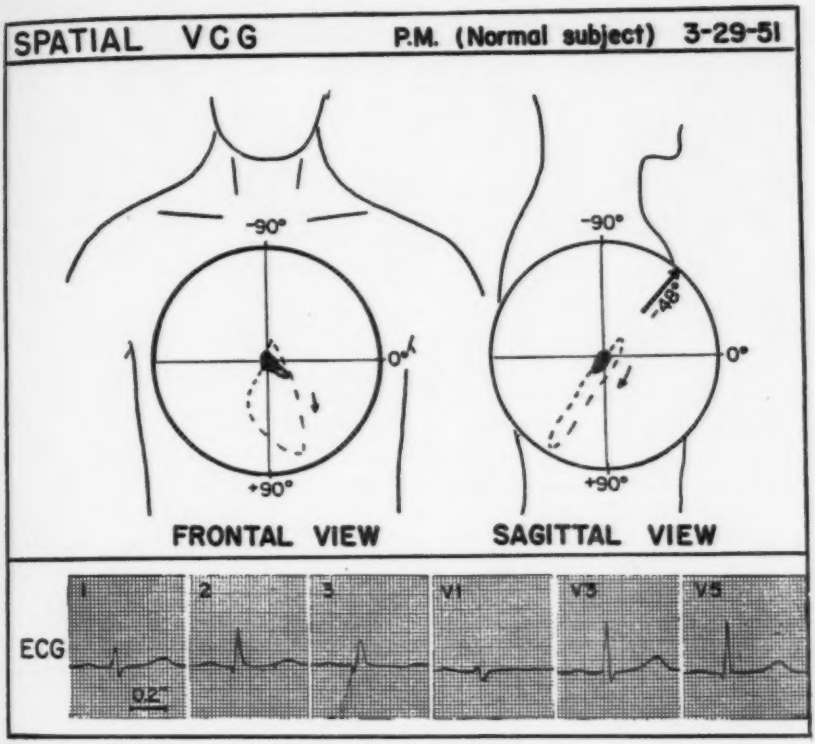

FIG. 1. Electrocardiogram and spatial vectorcardiogram of a normal subject, female, 20 years of age. The ECG shows a Q wave in leads II and III, and in V5. (Electrocardiograms were taken at a paper speed of 50 mm./sec., or double the routine speed, and standardization, not shown here, was 10 mm./millivolt in all leads.) Frontal and sagittal plane projections of the spatial VCG, photographed from the face of the cathode-ray tube, are shown; these should be regarded as two "views" of a single tri-dimensional VCG. The sagittal projection is shown as if seen from the patient's right side. The "null point" indicated by the intersecting horizontal and vertical lines in each view is analogous to the "isoelectric line" of the ECG. The P, QRS, and T deflections of the ECG each appear in the VCG as a "loop". At this low amplification the P and T loops are seen as blurs near the nullpoint, while the QRS complex is a larger, dashed, loop. The QRS loop appears as a discontinuous line because the cathode-ray trace is automatically blanked out at 4 millisecond intervals; this provides a means of timing the speed with which the loop is written. The dashes are made to appear wedge-shaped by modulation of the beam intensity, and point in the direction of rotation.

In this case, the QRS loop was written in a clockwise direction in both frontal and sagittal views. The direction of the initial QRS vector in the sagittal view is −48°.

backward and further to the left, then turns and moves upward again, and to the patient's right, returning to the nullpoint after a third smooth, gradual

turn. Thus the QRS loop has a more or less ellipsoid form, and lies roughly in one plane, which is seen almost on edge in the sagittal view. Although the three definite changes of direction, or inflections, in this loop correspond in a general way to the electrocardiographic "Q", "R", and "S" waves, it is apparent that this terminology is inadequate for vectorcardiography, because the portion of a loop which corresponds to a negative deflection in one ECG lead may appear as a positive deflection in another lead. In Figure 1, for example, the initial part of the QRS loop, which corresponds to the Q waves in leads II and III, is a part of the R wave in lead I. The early, middle, and late inflections described above are seen in almost all normal spatial QRS loops, and it may be useful in the future to develop a new vectorcardiographic terminology based on them.

When a Q3 is present in the ECG, it corresponds to the earliest portion of the spatial QRS loop, usually including the first inflection, and sometimes well beyond it. In the cases we have studied, the duration, relative size, and contour of this portion varied considerably, but it was not possible to distinguish between the normal subjects and the infarct cases on the basis of these characteristics. The only significant difference found between the two groups of patients was in the *direction* taken by the very earliest portion of the QRS loop. This initial part of the QRS loop travels away from the nullpoint in a fairly straight line for at least 0.012 seconds in almost all vectorcardiograms, and it is this segment that we have termed the "initial QRS vector." Its direction can be expressed as the angle made by its frontal or sagittal projection with the horizontal, designating angles above the horizontal as negative, and those below positive, as in Einthoven's schema for the angle α.

Comparing the normal records shown in Figure 1 with those from a case of myocardial infarction, shown in Figure 2, it can be seen that in the *frontal* projection the direction taken by the initial QRS vectors is approximately the same in each case. In this projection, no consistent difference between the normal and the infarction groups could be found, just as no distinguishing characteristics could be found in the standard or "unipolar" extremity leads, which lie in the frontal plane. In the *sagittal* projection, however, the initial QRS vector in Figure 1 is directed forward and upward ($-48°$), while in Figure 2 it has a more vertical direction ($-80°$). This difference was apparent in all cases studied, as shown in Figure 3. In all normal cases with a Q3 the direction of the initial QRS vector was between $+5°$ and $-62°$, while in the infarction cases it fell between $-68°$ and $-97°$. Overlapping between the two groups did not occur in this series, although borderline cases will doubtless be found as larger numbers of patients are studied.

A few patients whose electrocardiograms showed a Q3, and who had heart disease other than infarction, were also studied. In 12 patients with hyper-

tensive or arteriosclerotic heart disease the direction of the initial QRS vector in the sagittal view was the same as in our normal subjects, while in 4 out of 6 cases of chronic cor pulmonale it fell within the same range as our cases of myocardial infarction.

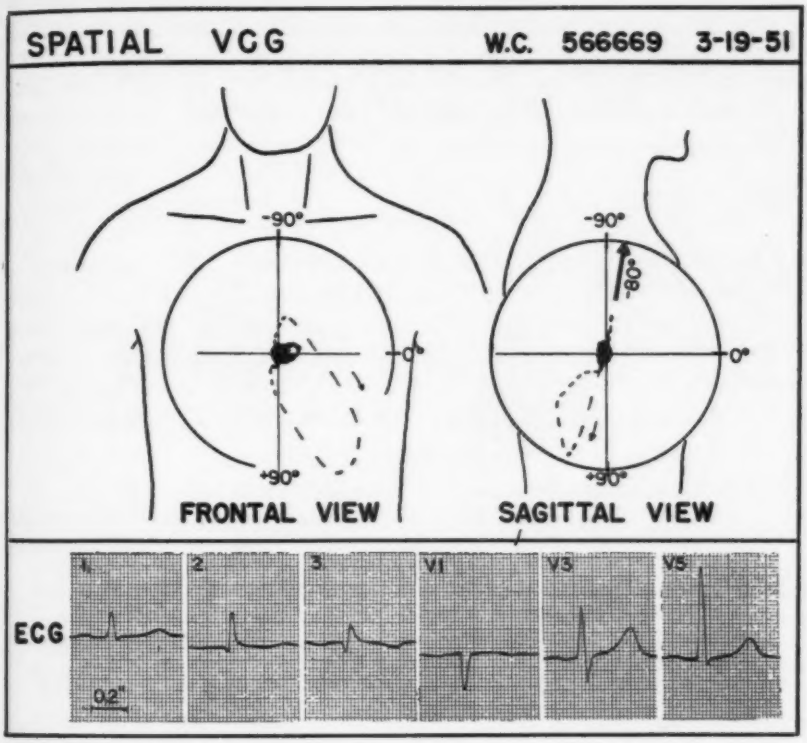

FIG. 2. Electrocardiogram and spatial vectorcardiogram of a male patient, 64 years of age, who suffered an acute myocardial infarction 9 months prior to this record. A Q wave is present in leads II and III of the electrocardiogram. As in Figure 1, the direction of rotation of the QRS loop is clockwise in both frontal and sagittal views. The direction of the initial QRS vector in the sagittal view is more nearly vertical (−80°) than in Fig. 1.

It should be pointed that all angular measurements of the spatial vectorcardiogram depend on the lead system and the standardizing factors used, and the limits shown in Figure 3 cannot be expected to apply to vectorcardiograms made under different conditions. However, from a small number of vectorcardiograms recorded with the Duchosal system of leads it appears that a similar differentiation between normal and abnormal Q3 deflections may be

possible with this and perhaps with other lead systems, although the specific measurements will be different from those reported here.

The physiological significance of these findings is not at all clear. The area of infarction in cases which develop a Q3 is usually in the postero-inferior wall of the ventricles, and the almost vertical direction of the initial QRS vector in

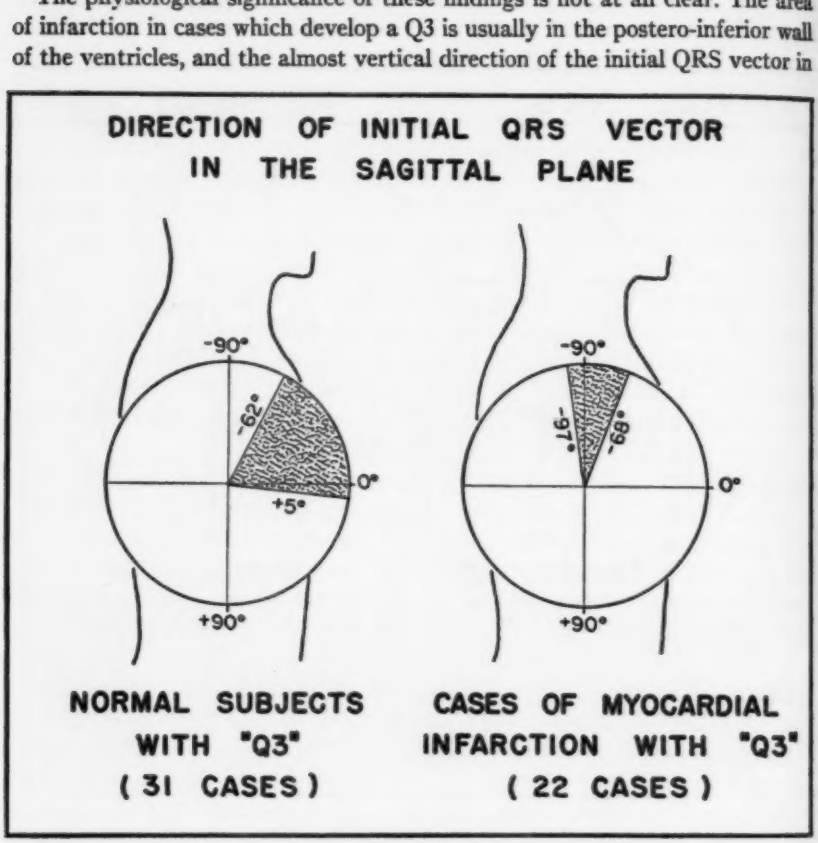

FIG. 3

our cases is in accord with the electrocardiographic theory that the Q waves of infarction, considered as vectors, point *away* from the region of the infarct. It is harder to interpret the fact that characteristic changes were apparent at the very beginning of ventricular activation, during the first 12 milliseconds of recorded depolarization This is difficult to reconcile with the theory that the Q waves of myocardial infarction represent the electrical negativity of the ventricular cavity, transmitted through the dead, electrically inactive, muscle of the infarct to the regions of the body nearest the injury (7). If this theory were true, one would expect the very earliest part of the QRS complex, which

has been assumed to be due to activation of the ventricular septum, to be unaffected by infarction unless the infarct involved the septum itself, and would not expect changes due to infarction to be apparent until the depolarization process had actually reached the injured area.

These findings are reported as purely empirical observations, and it should perhaps be emphasized that they do not depend on any of the specific theories of spatial vectorcardiography, which are still the source of considerable difference of opinion. The number of cases in this preliminary report is small, and not controlled by post-mortem observations; the conclusions must therefore be regarded as tentative and subject to verification or revision by future experience.

SUMMARY

Spatial vectorcardiograms were recorded from 53 persons who showed a Q wave in lead III of the electrocardiogram. Of these, 31 were normal subjects, and 22 were cases of previous myocardial infarction. The direction taken by the earliest portion of the QRS loop in the sagittal projection of the spatial vectorcardiogram was significantly different in the two groups. No other consistent distinguishing characteristic was noted.

ACKNOWLEDGEMENT

We are indebted to Dr. J. A. McCallum and Dr. T. M. Arrington for making possible the study of patients at the Ritchie State Hospital, Cascade, Maryland.

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THE EFFECT OF CORTISONE ON THE PRIMARY AND SECONDARY AQUEOUS AND ON CORNEAL VASCULARIZATION IN RABBITS*

S. RODMAN IRVINE, AND MARY DAILEY IRVINE

WITH THE TECHNICAL ASSISTANCE OF CAROL B. KASTNER

The Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University

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The mechanism by which ACTH and cortisone block inflammation is unknown. Very likely a multiplicity of factors is involved. It seemed possible that data on the protein content of the primary and the re-formed or secondary aqueous, and on the protein content of the aqueous as altered by "standard" corneal lesions, might give an insight into one or more of these factors.

Previous work (1) suggested that central corneal lesions might cause greater increase in the protein content of the aqueous than would peripheral lesions of equal severity. Cortisone may affect capillary permeability, or it may block the formation or the diffusion of the substance that stimulates capillary dilation and increased capillary permeability. Consideration of the fact that this "unknown" substance may seep into the aqueous and affect iris vessels led us to the present study of the aqueous as affording a possible medium for investigation of certain factors involved in the phenomena of inflammation.

The work to date is very incomplete, but certain preliminary observations are worth reporting at this meeting: namely,

I. The effect of cortisone on the protein content of the primary aqueous of rabbits.

II. The effect of cortisone on the protein content of the secondary aqueous.

III. Production of a "standard" minimal corneal lesion that will stimulate vascularization of the cornea if located at a certain critical distance from the limbus.

IV. The increase in aqueous protein resulting from standard corneal lesions.

V. The effect of cortisone on vascularization and healing of "standard" corneal lesions.

I. DETERMINATION OF THE EFFECT OF CORTISONE ON THE PROTEIN CONTENT OF THE PRIMARY AQUEOUS

Forty-six normal rabbits were used as controls.

Seventeen adult rabbits were given 10 milligrams of cortisone daily for four

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or more days before aqueous samples were withdrawn. The cortisone preparation used as the compound 11 Dehydro-17-hydroxycorticosterone-21-acetate, Merck's Cortone acetate, saline suspension, containing 25 mgs. per cc. and 1.5% benzyl alcohol as preservative.

The dosage used was decided upon because Dr. Alan C. Woods and Dr. Ronald Wood (2) found that this amount blocks the inflammation produced by injection of jequirity into the anterior chamber, and blocks the inflammation based on sensitivity to tuberculin; and that animals so treated show definite effects of cortisone administration, as evidenced by atrophy of the adrenal glands.

Aqueous samples were obtained after topical anesthesia of the cornea by instillation of a few drops of ½% pontocaine into the conjunctival sac. The eye was then proptosed with the fingers, and aqueous withdrawn. A very sharp 27 gauge needle and a Kinsey pipette were used for this procedure. The

TABLE 1

PROTEIN CONTENT OF PRIMARY AQUEOUS HUMOR (RABBITS)

Controls:		
Number of Rabbits	46	
Number of Aqueous Samples	169	
Average: Total Protein		47 mgs/100 cc.
Cortisone-treated:		
Number of Rabbits	17	
Number of Aqueous Samples	73	
Average: Total Protein		73 mgs/100 cc.

aqueous filled the pipette spontaneously. The average amount withdrawn was slightly less than 0.25 cc.

Total protein was determined by the Denis-Ayer method for determination of cerebrospinal fluid protein. This method is based on comparison of the turbidity produced by addition of sulphosalicylic acid to the aqueous with that produced by addition of the acid to a standard protein solution. The protein standard used as a basis for comparison was obtained from the Massachusetts General Hospital Spinal Fluid Laboratory. Readings were made in a photoelectric colorimeter.

The average protein is seen to be slightly higher in the samples from cortisone-treated animals. This is contrary to what we had expected. We offer no explanation, but call attention to two articles.

1. Valy Menkin (3) in the American Journal of Physiology for January notes an increased capillary permeability in the skin of rabbits treated locally with only 0.5 cc. of commercial cortisone acetate suspension. He attributes this to the aqueous vehicle in which the cortisone is suspended.

2. Peter Forsham (4) in the Bulletin of the University of California for

February notes that prolonged treatment, with cortisone or ACTH, suppresses the thyroid stimulating hormone of the pituitary, resulting in a hypothyroid state. Cerebrospinal fluid protein is known to be increased in myxedema, and the aqueous protein is very likely correspondingly increased.

Figure I exaggerates the apparent increase in protein in cortisone-treated animals over that in the controls. Over 60% of the samples from control animals showed protein values of less than 50 mgs. per 100 cc., whereas only 30% of the cortisone-treated animals had protein values in this range. On the other

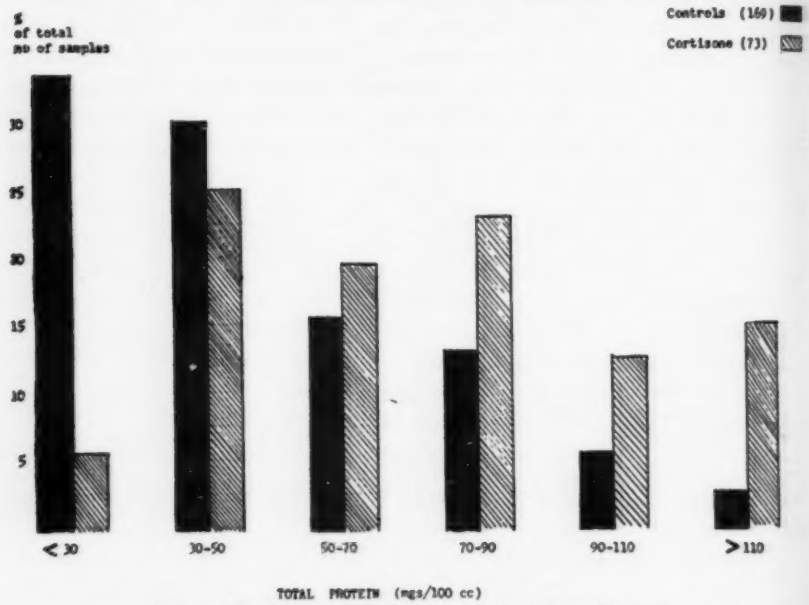

FIG. I. PROTEIN IN THE PRIMARY AQUEOUS OF RABBITS

end of the scale we see that 25% of the samples from cortisone-treated animals had protein over 90 mgs. per 100 cc. and only 7% of the control series were in this range.

The fact that the average total protein content of the samples from cortisone-treated animals was about 25 mgs. per 100 cc. higher than in samples from the control group probably has little significance. Future studies in which the effectivity of various adrenal cortical extracts is better controlled may reveal no significant difference. The important fact is that the protein content of the aqueous is not diminished in the cortisone-treated animals as one might expect if decreased capillary permeability were being maintained under cortisone treatment.

One may imagine that perhaps there might still be decreased capillary permeability, and that this might simply inhibit the resorption of protein from the anterior chamber, the protein accumulating and gradually reaching a value above that in the controls. This is unlikely in view of the results on secondary aqueous.

II. PROTEIN CONTENT OF THE SECONDARY AQUEOUS

The range of total protein values in secondary aqueous for any one time interval between primary and secondary samples was very great, in spite of the following precautions:

1. Only full grown rabbits were used.
2. The chamber was not emptied but the needle withdrawn after 0.20 cc. was removed.

TABLE 2

PROTEIN IN THE SECONDARY AQUEOUS HUMOR (RABBITS)

INTERVAL BETWEEN PRIMARY AND SECONDARY AQUEOUS	CONTROLS		CORTISONE	
	No. of Samples	Protein (average)	No. of Samples	Protein (average)
hrs.		*mgs/100 cc.*		*mgs/100 cc.*
1	(5)	3222		
2	(19)	964	(16)	1126
3			(6)	998
4	(6)	446		
6	(8)	485	(27)	235
7	(2)	227	(7)	122

3. The measured aqueous was promptly run into heparin solution to prevent clotting.
4. An attempt was made to remove aqueous at a uniform rate.

Considerable fibrin, and very variable amounts, are seen in the anterior chamber of rabbits after removal of primary aqueous. Sometimes a fibrin clot would plug the needle and a fair sample could not be obtained. In some cases considerable fibrin would be visible in the anterior chamber, and in others no fibrinogen would have come out of solution, an inconsistency making removal of aliquot samples impossible. Consistent with this variability due to clot formation is the fact that it is not unusual to see a fibrin clot in the anterior chamber of a rabbit in which the aqueous ray, by slitlamp examination, is negative. Samples removed six hours after the first puncture were most consistent, perhaps because the fibrin formed in the anterior chamber had disappeared by then, and more uniform samples were obtainable.

The points on the curve are averages of all the samples for the hour indicated. Although at each time interval the range of protein values was considerable, it is interesting and important that the highest value for the two-hour

interval in the control series was 2000 mgs. per 100 cc. and in the cortisone-treated was 1915. In other words, the total protein content of the secondary aqueous after two hours was practically the same in the cortisone-treated as in the control animals.

The values at the seven hour interval showed the lowest to be 142 in the control group and 91 in the cortisone-treated, and are again so much alike as

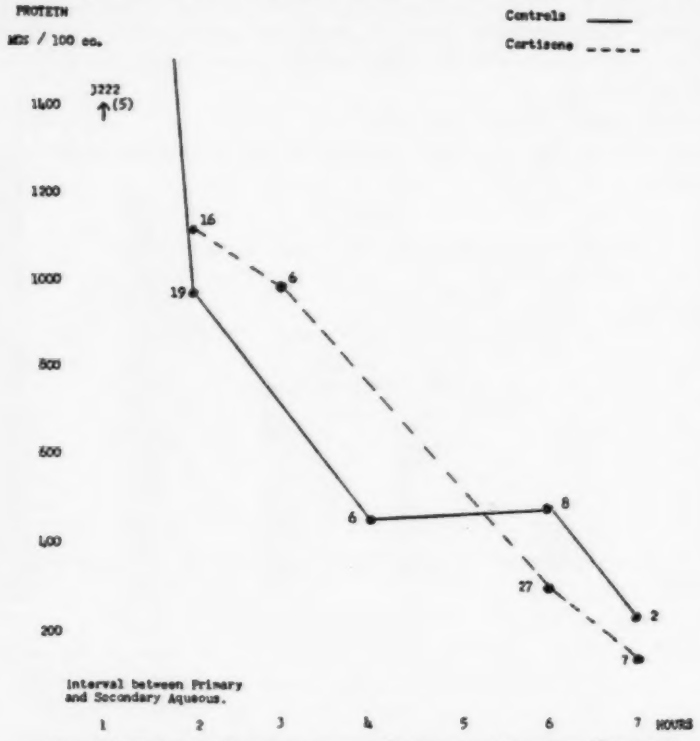

FIG. II. PROTEIN CONTENT OF THE SECONDARY AQUEOUS (RABBITS)

to indicate, as does the average for this interval, that the absorption of the protein from the plasmoid or secondary aqueous is much the same in both groups.

III. PRODUCTION OF A "STANDARD" MINIMAL LESION THAT WILL STIMULATE VASCULARIZATION OF THE CORNEA IF LOCATED WITHIN A CERTAIN CRITICAL DISTANCE FROM THE LIMBUS

Many investigators have attempted to produce "standard" corneal lesions in order to compare the extent of new-vessel formation as effected by various agents.

Campbell & Michaelson, (5) in the British Journal of Ophthalmology for April 1949 report results from cauterization by touching the cornea with a platinum wire heated to a uniform temperature by supplying constant voltage. They applied the cautery for about ten seconds daily for 10 to 14 days. The lesions were very comparable and vascularization depended on the distance of the lesion from the limbus.

The black circle represents the standard lesion. The concentric lines are placed at 1 mm. intervals. The shaded area indicates the theoretical shape of the area of infiltration.

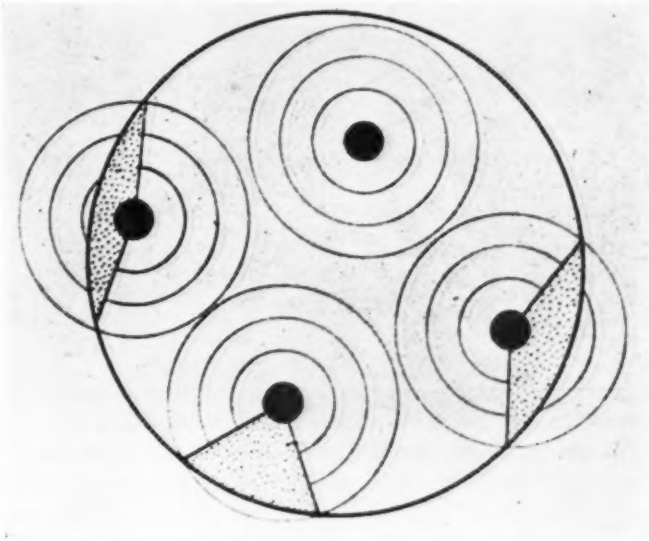

FIG. III. (FROM CAMPBELL AND MICHAELSON)

Beyond a critical distance of 4.0 mm. no vascularization resulted. When vascularization did occur the distance from the lesion to the basal angles of the triangular area of vascularization was relatively constant. These authors concluded that their findings could be accounted for by assuming that a factor, produced by the corneal lesion, diffuses equally in all directions, and becomes less effective the farther it is from the lesion. The amounts at the base angles of the triangle represent the minimal amounts of the factor capable of stimulating limbal vessels to bud. Beyond, it is in too low concentration to stimulate budding. Another concept is that there may be destruction of a substance that prevents invasion of vessels. Campbell and Michaelson conclude that their results suggest that, in the circumstances they describe, the new-vessel formation involves a factor released by the lesion and diffusing from the lesion.

We were anxious to produce lesions as uniform as possible in order to better evaluate the effect of cortisone on the aqueous protein as altered by a standard corneal lesion. Vascularization was to be used as a partial criterion of the uniformity of the lesions.

We first tried mechanical trephining and injection of zephiran solution into the cornea, but the lesions were not uniform.

We then tried cauterization by a platinum wire heated to constant temperature by constant voltage, application of diathermy current and of galvanic current, using both anode and cathode, and using different types of electrodes. Suitable lesions which became vascularized could be obtained by any of these methods.

TABLE 3

VASCULARIZATION OF CORNEA—WIRE CAUTERY

CONTROLS			CORTISONE-TREATED		
Rabbit	Distance from Limbus	Maximum Vascularization	Rabbit	Distance from Limbus	Maximum Vascularization
	mm.			*mm.*	
125	1¼	+++++			
123	2	+++	121	2	0
124	2	+++++	122	2	+
125	2½	++++			

Cautery

A wire cautery was heated to constant temperature by means of a constant electric current, and applied to the cornea at distances indicated on the chart. The cautery was touched to the cornea five times in rapid succession, in order that the average of the five applications might be the same for each lesion made. All lesions were examined daily with a slitlamp and the vascularization estimated by counting the vessels unless there was brush-like pannus formation, in which case the vessels were too numerous to count. Diagrammatic drawings of the lesions, indicating the extent and severity of the reaction, including notes on edema, flare, and vascularization, were made daily for the first five or seven days, while the appearance was undergoing the greatest change, and alternate days thereafter. This procedure of examination and recording of findings was followed in all the series discussed unless otherwise stated. In summarizing for the charts the lesions were graded as plus 1 to plus 5, plus 1 not meaning a fifth of that in plus 5, but rather a minimal vascularization, only 2 or 3 small vessels being seen. Plus 5, the maximum degree seen in this series, consisted of a thick brush-like pannus formation.

All cortisone-treated animals had been receiving 10 mgs/day for 4 or more days prior to production of the experimental lesions. Vascularization was observed usually on the 3rd day, progressing to reach a maximum between the

10th and 14th days. This maximum is recorded on the charts. Thereafter vascularization receded but in some cases has persisted up to the present time, 3 months after the lesions were made. The animals were maintained on cortisone for five weeks. During this period the character of the lesions and the vascularization were observed and form the basis of this report. The ultimate effects will be reported later.

The difference between the vascularization in the control animals and in those treated with cortisone is striking.

FIG. IV. Animal 125. Control: RE: Three plus vascularization; lesion 1.25 mm. from limbus.

Diathermy

A Walker diathermy unit and a Guyton flat electrode were used in producing these lesions. The cornea was dried before the electrode was applied and the application timed by stop-watch. In rabbit 62, lesion 1 mm. from the limbus, the total number of seconds was only 10, whereas in all other instances it was 20 seconds. Several applications were made in an attempt to standardize the lesion by getting an average pressure of application that would be the same for all lesions.

The control series shows the effect of the distance of the lesion from the limbus on the stimulation of vascularization. This corresponds well with the findings of Campbell and Michaelson.

Again, as in the cautery series, there is a striking difference between the vascularization of the controls and that in the cortisone-treated animals, the latter never showing development of more than 2 or 3 minimal vessels.

FIG. V. Animal 121. Cortisone. No vascularization; lesion 1.5 mm. from limbus.

TABLE 4

VASCULARIZATION OF CORNEA—DIATHERMY

CONTROLS			CORTISONE-TREATED		
Rabbit	Distance from Limbus	Maximum Vascularization	Rabbit	Distance from Limbus	Maximum Vascularization
	mm.			*mm.*	
62	1	+	101	1	0
62	1	++	101	1	0
61	1	++++	102	1	+
61	1	++++	102	1	+
62	1½	++	122	1½	+
62	2	++	120	2	+
123	2	++	121	2	0
124	2	+++	122	2½	+
125	2	+++	101	2½	0
64	4½	0	101	3	0
64	4½	0			

Galvanic

The highest degree of uniformity of lesions was obtained with the galvanic current, cathode electrode, a flat Guyton type of pin with a tip that had a diameter of about 0.2 mm., current of 2 milliamps applied for 55 seconds.

With this lesion, $3\frac{1}{2}$ mm. from the limbus seems to be the critical distance beyond which there is no stimulation of vascularization. The amount of hydroxyl ion produced in this lesion is very little, and is calculated to be equivalent to .001 to .01 cc. normal sodium hydroxide.

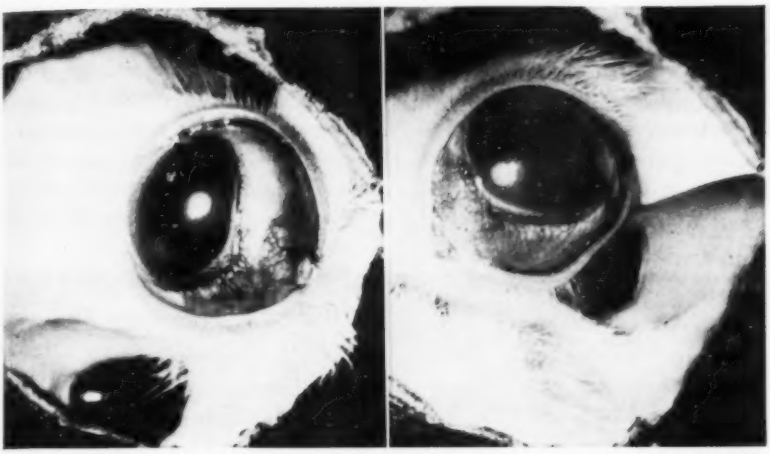

FIG. VI. Rabbit 134. Control (Lesion A) Appearance of lesion immediately after application of electrode: RE: Lesion 3.5 mm. from limbus; LE: Lesion 2.5 mm. from limbus.

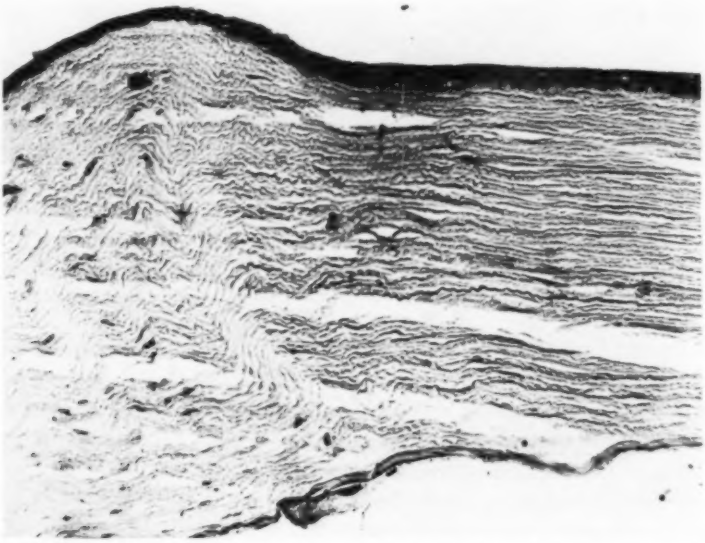

FIG. VII. Photomicrograph of corneal section taken 16 hours after application of galvanic current, 2 milliamps, 55 seconds, showing demarcation line at edge of lesion, and absence of corneal corpuscles.

This treatment produced a circumscribed white corneal opacity, about 2 mm. in diameter, deep in the corneal layers. It caused minimal damage to the

epithelium and was least affected by possible variation in the pressure of application. This pressure could be further standardized by fixing the animal's head in a clamp-holder and applying the electrode with a micromanipulator. As this refinement would require general anesthesia it was considered impractical for our purposes as compared with the simple procedure of local anesthesia and manual application of the electrode. The lesion seemed particularly well suited for evaluation of the effect of cortisone as it produced injury to the stroma of the cornea primarily, with minimal effect on the epithelium, and we judge from

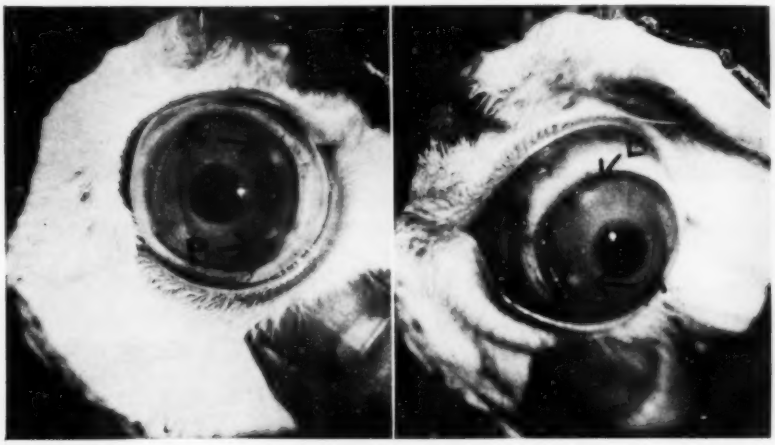

FIG. VIII. Rabbit 134. Control. (A) Appearance 12 days after lesion made: RE: Lesion 3.5 mm. from limbus, shows no vascularization; LE: Lesion 2.5 mm. from limbus shows two plus vascularization. (B) Second lesion, appearance 6 days after lesion made: RE: Lesion 1.5 mm. from limbus, four plus vascularization; LE: Lesion 1.5 mm. from limbus, four plus vascularization.

the literature that the most spectacular effects of cortisone are in conditions wherein the pathology involves primarily connective or collagenous tissue.

Here the effect of distance from the limbus is demonstrated particularly well, both in the controls and in the cortisone-treated animals, and again, the inhibition of vascularization by cortisone is demonstrated.

In the first part of the series the lesion was minimal, from 20 seconds application of the electrode, and very minimal vascularization was seen in 4 of the 5 controls and no vessels at all in the cortisone-treated animals.

In the group with more severe lesions, from 55 seconds application of the electrode, there was pannus formation in both eyes of one cortisone-treated animal, and in seven of the control eyes.

In every series of experiments, whether the lesion was by wire cautery heated to constant temperature, or by diathermy or galvanic current, the

FIG. IX. Rabbit 131. Cortisone: RE: Lesion 1.5 mm. from limbus, no vascularization; LE: Lesion 3.0 mm. from limbus, no vascularization.

TABLE 5

VASCULARIZATION OF CORNEA—GALVANIC CAUTERY

CONTROLS			CORTISONE-TREATED		
Rabbit	Distance from Limbus	Maximum Vascularization	Rabbit	Distance from Limbus	Maximum Vascularization
10 sec.					
	mm.			*mm.*	
62	1	+	18	1	0
62	1	+	102	1	0
62	1	+			
62	1	+	24	1½	0
20	1½	0	14	1½	0
55 sec.					
65	1½	++++	130	1½	++++
133	1½	++++	130	1½	++++
133	1½	++++	131	1½	+
134	1½	++++	131	1½	0
134	1½	++++	132	1½	+
135	1½	++++	132	1½	++
135	1½	++++			
61	2	+++			
134	2	+++	130	3½	0
133	3½	+	130	3½	0
133	3½	+	131	3½	0
134	3½	+	131	3½	0
135	3½	0	132	3½	0
135	3½	0	132	3½	+

production of vascularization of the cornea was definitely greater in the control animals than in those receiving cortisone. When vascularization was not completely inhibited in the cortisone-treated animals, it was delayed longer than in the controls and the maximum extent of vascularization was diminished.

TABLE 6

LIMBAL AND CENTRAL CORNEAL LESIONS (GALVANIC)

	SLIT-LAMP FLARE				PROTEIN (MGS. PER 100 CC.)	
	3 Hours		6 Hours		6 Hours	
	Limbal	Central	Limbal	Central	Limbal	Central
Controls						
A	+	+	0	0	64	100
B	++	++	0	++	65	225
C	+++	+++	++	++	600	557
D	++	++	++	++	1406	2132
E			0	0	117	71
Cortisone						
F	++	+	+	+	224	
G	+	+	0	0	60	24
H	+	++	0	0	127	104
I	+	Clot	0	0	119	100

IV. THE INCREASE IN AQUEOUS PROTEIN RESULTING FROM STANDARD CORNEAL LESIONS

Up to this time we have determined the aqueous protein in samples from eyes with central lesions and eyes with limbal lesions, using this "standard" galvanic lesion, in only one series of 5 control and 4 cortisone-treated animals. We hoped to find a difference in response to the lesions reflected in the protein content of the aqueous.

The animals were observed hourly by slitlamp. At the end of six hours the flare in the anterior chamber was definitely diminishing and aqueous samples were withdrawn.

The limbal and central lesions, contrary to our expectations, had about the same effect on increasing the aqueous protein. Nevertheless, it is still our impression from observing other series of limbal and central lesions, that the central lesions do tend to produce more aqueous flare.

If we considered animals A, B and E of the control series and the 4 cortisone-treated animals we would say that the aqueous protein values were the same in both groups. In fact they average 107 mgs. per 100 cc. and 108 mgs. Control animals C and D have unusually high proteins and whether this is of any significance or not cannot be stated from the meagre data of this last experiment.

V. THE EFFECT OF CORTISONE ON VASCULARIZATION AND HEALING OF STANDARD CORNEAL LESIONS

Factors affecting vasculogenesis are under investigation. As yet we have no controlled observations correlating edema with vascularization or the effect of cortisone on healing or scar formation. Cogan (6) has postulated a theory of vasculogenesis, that reduction in the tissue compactness of the corneal stroma, altering local mechanical pressure relationships, relieves tissue tension, allowing dilation of adjacent capillaries, subsequent capillary aneurysms, hemorrhage and proliferation of endothelium around the hemorrhage. Many of our cortisone-treated animals showed edema of the cornea, adjacent to the limbus, without evidence of vascularization. Small diathermy lesions appear to produce less edema than do galvanic lesions, and yet vascularization was certainly not less with the diathermy lesions.

Often vessels will proliferate toward the entrance of a needle track placed near the limbus. Such lesions have minimal edema.

These observations indicate that factors other than edema, such as necrosis of tissue, may be important in stimulation of vascularization.

The immediate healing of lesions in the cortisone-treated animals seems to be delayed somewhat but the ultimate healing and scar formation, a month after the lesion was made, were about the same as in the controls.

In this connection it must be realized that the lesions we produced were minimal, and it is quite possible that more severe lesions, although masking the difference in the tendency for new-vessel formation [as in the experiments of Rich (7) and of Leopold (8)] might exaggerate the differences in healing time and scar tissue formation. A few of the lesions in our cortisone-treated series gave such an indication, the tissue healing in these being greatly delayed, the wound becoming covered with irregular epithelium and there being reduced vascularization with only slight fading of the opacity.

On the other hand, there were some control animals in which the lesion seemed to heal very rapidly, the opacification of the cornea becoming minimal, but proliferation of vessels was exaggerated, forming a medusa-like cluster of vessels with concomitant supporting tissue on top of what appeared to be a minimal degree of deep opacity from the original lesion. This may represent excessive healing response. It is quite possible that the organism's immediate reaction to injury (alarm reaction), and repair processes are balanced by the adreno-corticotropic hormones and that their clinical administration, in the future, will be directed toward maintenance of the best balance for definitive healing of lesions.

SUMMARY

Cortisone does not cause diminution of the protein in the primary aqueous.

Cortisone appears to have no effect on the level of protein in the secondary aqueous.

The effect of cortisone on the increase in aqueous protein resulting from "standard" corneal lesions is inconclusive.

Corneal vascularization resulting from minor injury by heat, diathermy or galvanic cautery, is definitely inhibited by cortisone.

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TISSUE CULTURE STUDIES ON LIVER CELLS OF TUBERCULIN SENSITIZED ANIMALS IN THE PRESENCE OF TUBERCULIN (PURIFIED PROTEIN DERIVATIVE)*

JOHN J. BUCKLEY, SONJA M. BUCKLEY, AND MARGARET L. KEEVE

The Division of Laboratories and Research, New York State Department of Health, Sloan-Kettering Institute for Cancer Research
and
The Division of Experimental Chemotherapy, Sloan-Kettering Institute for Cancer Research, New York, New York

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In 1932 Rich and Lewis (1) and later Aronson (2, 3), and Moen and Swift (4), clearly demonstrated in tissue culture that one must distinguish between a tuberculin type and an anaphylactic type of hypersensitivity. One of the differences is that the cells of an animal with tuberculin type of hypersensitivity are killed *in vitro* by contact with the specific bacterial protein, whereas such cells from an animal with the anaphylactic type of hypersensitivity are not. It is assumed today that the tissue death observed *in vivo* in the Arthus reaction results primarily from impairment of nutrition by vascular damage, whereas in the tuberculin type, the cells at large are sensitive.

The cells studied *in vitro* by others up to the present time were spleen, blood leucocytes, and bone marrow, in other words, cells derived solely from the mesoderm. The question of the sensitivity of isolated epithelial cells of the sensitized body has not been previously examined by means of tissue culture. *In vivo*, Long (5) has observed necrosis of testicular tubules in guinea pigs following the injection of tuberculin into testes previously infected with tubercle bacilli. Stewart (6), subsequently, reported similar results in a study on "focal tuberculin hypersensitiveness in an infected organ previous to a general sensitization." He emphasized the lack of oedema in the early tuberculin reactions, the "marked distinguishing feature" of which was necrosis of testicular tubules prior to any histological evidence of vascular damage. However, *in vitro* studies of isolated cells, as has been pointed out by Rich (1), are the only adequate means of determining whether the injurious effects of the specific antigen are due to a direct action upon the cells.

In 1949, Buckley et al. (7) demonstrated that epithelial hepatic cells from Arthus-sensitized rabbits are unaffected by contact with the specific antigen in tissue culture, both in the presence and absence of specific antibody. The

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present *in vitro* study deals with the sensitivity of isolated epithelial cells of a tuberculin hypersensitive animal to the specific antigen.

EXPERIMENTAL METHODS

Adult male albino rabbits, weighing about 2500 grams, were used. Hypersensitivity was induced by five weekly injections of an antigen consisting of acetone-dried virulent human tubercle bacilli incorporated in paraffin oil. Skin tests were carried out one week after the last injection of antigen. Only rabbits reacting with a marked positive tuberculin test (diameters of areas of redness and oedema: from 20 mm. up to 49 mm.; elevation of skin observed) to the intradermal injection of 0.2 ml. of a 1:5 dilution of Old Tuberculin were used. An interval of one week was allowed to elapse between the skin test and the experiment. At that time a piece of liver was removed by biopsy using aseptic precautions under ether anesthesia, and was used for tissue culture. For every experiment in which liver from a tuberculin hypersensitive rabbit was cultured, a control experiment was carried out in which liver from a normal rabbit was used.

Purified Protein Derivative (P.P.D. No. 099503-D) obtained through the courtesy of Parke, Davis and Company was used as the specific protein. This product did not contain any salts of the medium. It was indicated by the manufacturer and experimentally verified in this laboratory that 0.1 cc. of the first test dose of P.P.D. (Tuberculin) which represented 0.00002 mg., was the equivalent of 0.1 cc. of a 1:10,000 dilution of Old Tuberculin. A concentrated solution (2 mg. P.P.D. in 1 cc. of physiological saline) equal in strength to undiluted Old Tuberculin was prepared at the beginning of the study.

TISSUE CULTURE METHODS

The methods were essentially the same as described previously (7). The media used were prepared in two parts. Part I consisted of two parts of balanced salt solution, Gey (8), one part of chicken embryo extract, one part of horse serum, and one part of serum of a normal or allergic rabbit. Part II consisted of two parts of balanced salt solution which contained measured amounts of P.P.D., one part of chicken plasma and one part of plasma of a normal or allergic rabbit. Each part was thoroughly mixed. In each experiment a piece of liver removed at biopsy was minced, under aseptic precautions, with detachable knife blades[1] into pieces approximately 0.5 mm. in diameter. Four of these pieces were placed on sterile slides and one drop of Part I medium added, followed by one drop of Part II, whereupon clotting resulted promptly. The slide was then inverted and sealed with vaseline to a metal ring attached to a slide with vaseline. The cultures, placed in an incubator maintained at 35°C., were examined daily beginning with the fourth day. At the end of six days the cultures were fixed in Vandergrift's solution (9) and stained with dilute Giemsa solution as described previously (7).

In ten experiments, media containing serum and plasma from normal or allergic rabbits were used so that the cells of the sensitized and the control animals could be studied in the presence and absence of the specific antigen, and in the presence and absence of antibody-containing rabbit serum and plasma. Table I shows the outline of a typical experiment and the results obtained in the different groups.

EXPERIMENTAL RESULTS

The morphology of the outgrowing cells has been described (7).

Our experiments, which include hundreds of cultures of liver cells, show

[1] Bard-Parker Detachable Type Blades No. 11.

clearly that the hepatic epithelial cells of a sensitized rabbit are much more sensitive to the effects of P.P.D. than those of a normal rabbit. Figures 1 to 4 are representative of growth of liver cells of allergic and normal rabbits with and without P.P.D. The outgrowth was either markedly inhibited or the cells

TABLE I

Effect of Purified Protein Derivative (P.P.D.) on Liver Cells

GROUP	NUMBER CULTURES	WASHED LIVER CELLS FROM	PLASMA + SERUM FROM	CONC. P.P.D. (2 MG/ML) IN CULTURE	GROWTH	CONDITION OF CELLS
I	30	Normal rabbit	Normal or allergic rabbit	—	Good	Good within six days
II	30	Normal rabbit	Normal or allergic rabbit	1:60	Good	Good within six days
III	30	Allergic rabbit	Normal or allergic rabbit	—	Good	Good within six days
IV	30	Allergic rabbit	Normal or allergic rabbit	1:60	None or slight	Most cells dead within six days

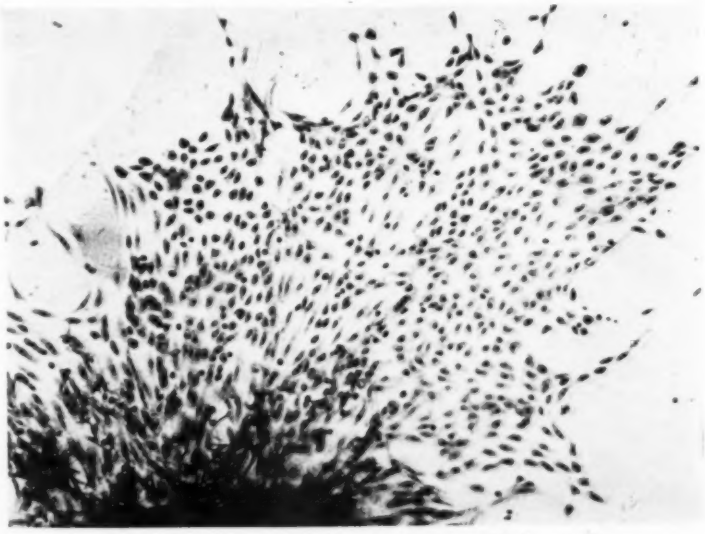

FIG. 1. NORMAL LIVER CELLS WITHOUT P.P.D. ×65

were killed by amounts of tuberculin in which normal cells grow without being injured. Since P.P.D. combined with plasma from allergic animals had no more effect on either washed sensitized or washed normal cells than P.P.D. combined with plasma from normal animals, it appears that the presence of a specific humoral antibody is not required in the allergic reaction. The

FIG. 2. NORMAL LIVER CELLS WITH P.P.D. ×65

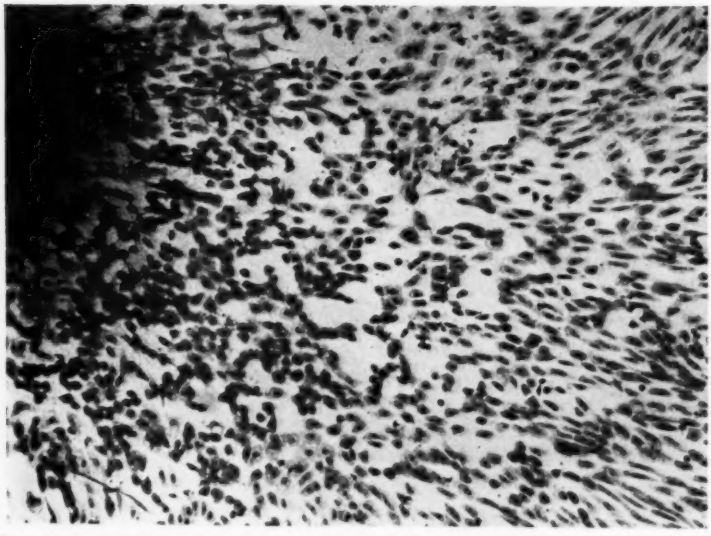

FIG. 3. LIVER CELLS FROM A HYPERSENSITIVE ANIMAL WITHOUT P.P.D. ×65

rôle of complement, if it plays any rôle, was not determined in these experiments.

CONCLUSION

In the tuberculin type of hypersensitivity, not only the cells derived from mesoderm, but also hepatic epithelial cells are more sensitive to the protein of the tubercle bacillus than are normal cells. Hepatic epithelial cells from a rabbit sensitized to tubercle bacilli showed lack of growth, cellular injury and necrosis upon exposure *in vitro* to tuberculin. Specific humoral (circulating) antibodies are not necessary for the allergic reaction. We are at present examining the question of whether or not complement plays a rôle in this phenomenon.

FIG. 4. LIVER CELLS FROM A HYPERSENSITIVE ANIMAL WITH P.P.D. ×65

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NON-TRAUMATIC AORTIC VALVE RUPTURE

DOUGLAS CARROLL*

Department of Medicine, The Johns Hopkins University School of Medicine and Hospital

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Since Howard's extensive review of the literature and report of a case of aortic valve rupture in 1928 (1), little has been written about this striking condition (2). Furthermore, the interest has been in those cases associated with trauma and with muscular exertion. The present report concerns 24 cases of non-traumatic aortic valve rupture, proved at autopsy. Fifteen cases were associated with bacterial endocarditis, seven with syphilis, one with arteriosclerosis, and one was idiopathic.

BACTERIAL ENDOCARDITIS

Bacterial endocarditis is the most common cause of rupture of the aortic valve. Thayer (3) has pointed out that certain bacteria, especially the pneumococcus and gonococcus, cause ulceration and destruction of the valves in bacterial endocarditis. Perforation of the belly of a valve cusp without actual rupture of the cusp margin occurred in one-half of the cases reported here. Cultures, available in 10 of the 15 cases, were Pneumococcus type XII in 2 cases; and, in one case each, Pneumococcus type XIV, type XXII, Streptococcus salivarius, Streptococcus mitus, B. Streptococcus Group D, alpha Streptococcus, a Gram negative coccus, Staphylococcus aureus and an untyped Pneumococcus.

Rupture of the aortic valve in bacterial endocarditis is extremely important since cure of the infection with antibiotics is of little use, if extensive destruction of the valve has occurred. Two of these patients were cured of the infection, but died of heart failure due to perforation of the aortic valve.

Four cases had rupture or perforation of 2 aortic cusps. The aortic leaflet of the mitral valve was perforated in two cases. Two cases had mycotic aneurysms, one of which led into the right atrium.

Diagnosis of a ruptured or perforated cusp is extremely difficult because of the well known tendency of murmurs to change in bacterial endocarditis. In only one patient was the diagnosis of a rupture made correctly.

Case 1: N. T. (J.H.H. History No. 312038), a 57 year old circuit court Judge came to the hospital in January, 1944, complaining of weakness, fever and weight loss of one year's duration.

There was a history of rheumatic fever at the age of 10 years and a heart murmur for many years prior to admission.

In January, 1943, following an upper respiratory tract infection, there was intermittent

fever, night sweats, marked weakness and weight loss. A diagnosis of subacute bacterial endocarditis was made at another hospital, but because there was no improvement, he was referred to the Johns Hopkins Hospital in January, 1944.

Physical examination at this time showed a temperature of 101° F., a pulse rate of 126, respirations of 30 per minute and a blood pressure of 120/80. There were numerous moist rales at both lung bases. The heart was slightly enlarged. The second pulmonic sound was accentuated. There was a loud harsh systolic murmur at the apex transmitted to the axilla. The first sound at the apex was feeble. The pulse was regular with a wide excursion but was not collapsing in quality. The liver and spleen were not felt. There were no petechiae; there was no ankle edema or digital clubbing.

There was moderate anemia; the leucocyte count was 4,300 with 90 per cent polymorphonuclear cells. The blood culture was repeatedly positive for alpha streptococci.

He was discharged on 6 Gm. of sulfadiazine daily and continued to feel fairly well at home until there was sudden paresis of the right side 10 days before the second admission.

He returned to the hospital on March 16, 1944 for penicillin therapy. There was little change in the physical examination except that the spleen was easily palpable, and there was some difficulty in control of motion of the right hand. The blood pressure was 120/80, and the heart sounds and murmurs were unchanged.

Late on the second hospital day there was sudden pulmonary edema. Examination showed that the pulse was now collapsing with the blood pressure 132/50/0; pistol shot sounds were heard over the femoral vessels, and a to-and-fro murmur was heard over the aortic area. A diagnosis of ruptured aortic cusp due to bacterial endocarditis was made.

Although the response to digitalis initially was good, the signs of heart failure progressed, and he died 2 weeks after the rupture of the valve.

Postmortem examination showed that there was 500 cc. of clear yellow fluid in both pleural cavities. The heart weighed 400 Gm. and all heart cavities were dilated without much hypertrophy. There were vegetations in the left auricular appendage. There were small fresh vegetations on the auricular surface of the aortic leaf of the mitral valve. The chordae tendinae were normal. There was a perforation of the left aortic cusp 5 x 5 mm. in diameter. The other cusps were normal. The lungs showed pulmonary edema; the liver was not enlarged. There was an acute splenic tumor; the spleen weighed 650 Gm. There were infarcts of the kidney, cerebellum and frontal cortex. There was arteriosclerosis of the aorta, renal and coronary arteries. There was no microscopic evidence of old or fresh rheumatic heart disease.

Comment: This is the only patient with bacterial endocarditis in whom a diagnosis of aortic cusp rupture was made during life. It is of interest that although there was a history of rheumatic fever in childhood and a murmur in adult life, no evidence of rheumatic heart disease was found at autopsy.

SYPHILIS

Seven patients had ruptured valves associated with syphilis of the aorta or aortic valve. Although all the patients had syphilitic aortitis, not all had typical syphilitic involvement of the aortic valve commissures and valve cusps. Nevertheless, there was dilatation of the aortic ring, and the valve cusps did not come into exact apposition during closure and did not support each other to prevent regurgitation. Consequently, the cusps were under stress and tended to be stretched during diastole. This may explain why ruptures occur with

syphilitic aortitis. Three patients with bacterial endocarditis also had syphilitic aortitis and syphilis of the aortic valve, but the rupture at autopsy appeared to be caused by the endocarditis rather than by syphilis.

One unusual finding occurred in two patients of this group. Small holes were present in the valve cusp above the line of closure of the valve. In one case the tear was through this area.

Case 2: J. S. (J.H.H. History No. 541176) a 43 year old Negro entered the hospital September 30, 1950 for severe shortness of breath.

In 1926 he had had a chancre which was untreated.

About February, 1950, he developed exertional dyspnea, anorexia and weight loss and in May, 1950 right upper quadrant discomfort. Early in June the patient noted the sudden onset of a rasping sensation in his chest. Shortly after this episode paroxysmal nocturnal dyspnea ensued.

Examination at this time showed the blood pressure to be 150/50, with peripheral signs of aortic insufficiency. The heart was enlarged to the anterior axillary line, and there was a diastolic thrill felt to the left of the upper sternum. A grade 2 systolic murmur could be heard in the aortic area and at the apex. The heart sounds were obliterated by the murmurs. The liver was palpable below the umbilicus. There was no peripheral edema. The serological test for syphilis was positive in a titer of 16 units. The electrocardiogram was not remarkable. The heart was grossly enlarged by fluoroscopy. The enlargement was due almost entirely to the left ventricle.

The patient was thought to have a ruptured aortic cusp with syphilitic involvement of the aorta and valve and was treated with 10 million units of penicillin in addition to digitalis, diuretics and a low salt diet.

Despite these measures, there was slowly progressive dyspnea, orthopnea and nocturnal dyspnea necessitating his admission to the hospital September 30, 1950.

At this time there was extreme orthopnea and dyspnea. The blood pressure was 160/50, and there were peripheral signs of aortic insufficiency. There was no change in the cardiac enlargement or in the murmurs, but there were moist rales at the lung bases. The liver was enlarged below the umbilicus, but there was no peripheral edema.

There was three plus albuminuria; the non-protein nitrogen was 137 mgm. per cent. Signs of cardiac failure and uremia increased, and the patient died on the fifth hospital day.

At autopsy the heart weighed 850 Gm. There were small fenestrations in the pulmonic valve leaflets under the free margin near the attachment to the commissures. The right coronary cusp of the aortic valve was thickened with a rolled free margin. There was an old tear of 6 mm. near the right side of the cusp. The margins of this tear were rounded. On the left side of the same leaf there was a tear at the site of fenestrations similar to those present in the pulmonic valve. The edges of this tear were sharp, and it appeared to be of more recent development. There were fenestrations of one of the other aortic valve leaflets. The other valves were normal.

The left ventricular wall was 10 to 14 mm. in thickness, the right ventricular wall 3 to 5 mm. There was syphilitic aortitis. The lungs showed pulmonary edema. The liver weighed 1850 Gm., and there was chronic passive congestion.

Comment: There were peculiar fenestrations in the pulmonic and aortic valve leaflets. The learge tear in the right coronary cusp was in the area of the fenestrations in the valve cusp.

It is remarkable that there were two ruptures of the cusp, one apparently

older than the other. The heart was tremendously enlarged. Possibly the smooth rounded tear was older than the sharp tear.

This patient noted the sudden onset of a murmur in the chest concomitant with the increasing severity of the symptoms.

Case 3: E. N. (J.H.H. History No. 536530), a 67 year old Negro, was first seen in the hospital on May 2, 1950, with a fractured left maxilla. Shortly before coming to the Accident Room, he had been attacked with a hammer and knocked unconscious by a blow to the left maxilla. The fracture was reduced and fixed with the extraction of one tooth.

On May 22, 1950, there was sudden paroxysmal nocturnal dyspnea with severe orthopnea and a cough productive of pink sputum.

Examination shortly after this episode showed a severely dyspneic and orthopneic man with a blood pressure of 160/44 and peripheral signs of aortic insufficiency. There was generalized thickening of the arteries. The point of maximal cardiac impulse was localized just beyond the left mid-clavicular line in the fifth intercostal space. There was a diastolic thrill to the left of the upper sternum. A grade 3 systolic murmur and a grade 4 "wood-sawing" diastolic murmur replaced the heart sounds over the entire precordium. The liver was palpable 5 cm. below the right costal margin. There was moderate ankle edema.

The Wassermann reaction was negative. The electrocardiogram was normal. The heart size was normal on x-ray, and the lungs showed a diffuse generalized infiltration compatible with congestive heart failure.

The etiology of the cardiac failure was believed to be aortic insufficiency, probably due to arteriosclerosis of the aortic valve. The possibilities of rupture of the valve at the time of his injury and of syphilitic aortic insufficiency were mentioned but considered unlikely.

There was a good response to digitalis, a low salt diet and diuretics.

For several months he was able to work but the heart failure gradually increased in severity.

Early in November, 1950, he was admitted to the hospital in severe cardiac failure. There was no response to the usual measures for cardiac failure, and he died November 14, 1950.

Autopsy showed that the heart weighed 370 Gm. The heart valves were normal except the aortic valve where the right coronary cusp was ruptured near the posterior commissure. In addition there was a perforation of the right coronary cusp 3 by 12 mm. at the opposite side of the cusp from the rupture (Fig. 1). The left ventricular wall measured 24 mm. in thickness, and the right ventricle wall was 9 mm. thick. There was pulmonary edema, particularly of the lower lobes. The liver weighed 1100 Gm. and showed only slight evidence of chronic passive congestion. There was syphilitic aortitis, but little change in the aortic commissures.

Comment: This patient had both a perforated and ruptured valve. The perforation was probably of longer standing than the rupture. It is possible that the rupture dated from the trauma to the face.

Case 4: L. A., (J.H.H. History No. 130176), a 34 year old Negro, entered the hospital January 17, 1938, complaining of shortness of breath and ankle swelling of 5 weeks' duration.

In 1916 he came to the hospital for tonsillitis and was found to have a positive Wassermann reaction. Examination at this time showed the remains of a papular skin eruption. The heart and lungs were normal. He received several injections of arsphenamine and one of bismuth subnitrate, but failed to return to complete the course of treatment.

He felt well until 5 weeks before admission when exertional dyspnea began. The dyspnea increased followed by swelling of the ankles. Paroxysmal nocturnal dyspnea ensued with orthopnea, and he reported to the hospital.

The temperature was 100.4° F., the pulse 104, the respirations 24, and the blood pressure 114/94. There were medium moist rales over the lung bases posteriorly. The point of maximum cardiac impulse was 11 cm. to the left of the midline in the fifth intercostal space. There was a diastolic thrill at the apex. The heart sounds were obliterated by a to-and-fro murmur over the entire precordium, the diastolic component being the louder. The murmur

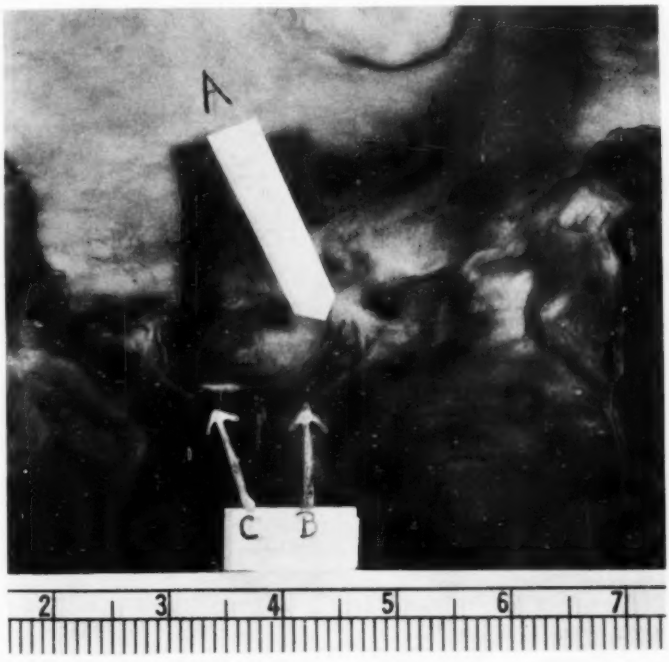

FIG. 1. Aortic valve of Case 3 showing at A the commissure between the left and right coronary cusps. B is the perforation and C the tear in the right coronary cusp.

was loudest at the apex, distant at the base. There were peripheral signs of aortic insufficiency. There was moderate sacral and ankle edema, but the liver was not palpable.

The Wassermann reaction was positive. The heart was enlarged by x-ray. The electrocardiogram showed a normal axis with occasional auricular premature beats.

There was a good response to digitalis and salt restriction. The possibility of a ruptured aortic valve cusp was considered because of the short course of the illness and the rumbling diastolic murmur at the apex.

Despite the improvement in cardiac status, he became restless, agitated and finally frankly psychotic. The pulse became weak, and he died February 22, 1938.

On postmortem examination the right pleural space contained 550 cc. of clear yellow fluid. The left pleural space contained 250 cc. The pericardial sac contained 150 cc. The heart

was tremendously dilated without much hypertrophy. It weighed 480 Gm., the right ventricular wall being 4 mm. in thickness and the left ventricular wall 10 mm. in thickness.

The heart valves were normal except for the aortic valve. The right coronary cusp showed a series of small fenestrations above the line of closure. In the left cusp this process was accentuated. There were three widely patent small fenestrations above the line of closure of the valve. At the end of this cusp opposite the fenestrations, there was a tear extending

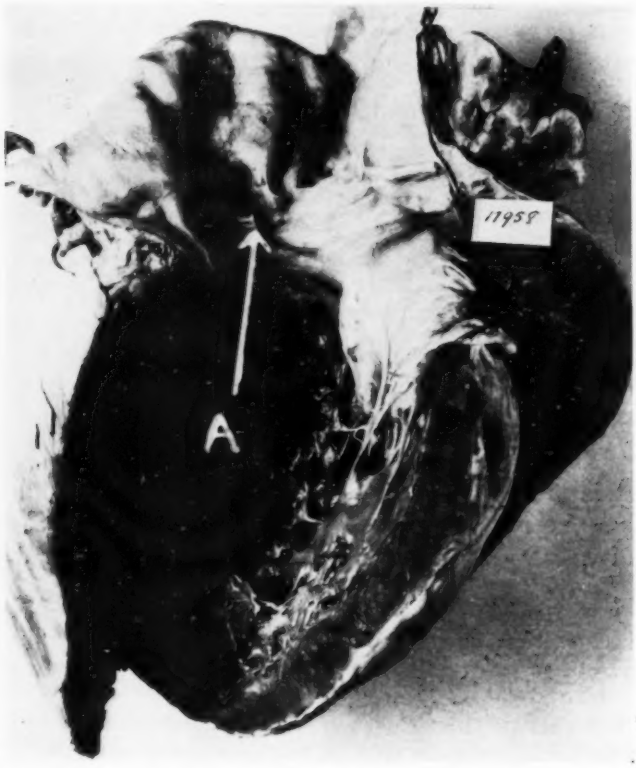

FIG. 2. Aortic valve of Case 5 showing at A the tear of the right coronary cusp.

from the cusp margin to the base. The tear was covered with endothelium, and the surface was rounded and smooth. There was syphilitic aortitis.

There was chronic passive congestion of the lungs and liver. The liver weighed 1900 Gm.

Comment: The short course and the loud murmur, together with signs of aortic insufficiency and a loud diastolic murmur suggested the possibility of a ruptured cusp in this patient. The syphilis had been inadequately treated. The fenestrations in the cusps probably contributed to the weakening and rupture of the valve.

Case 5: A. W. (J.H.H. History No. 251992), a 44 year old Negro, was admitted to the hospital on February 15, 1942, complaining of dyspnea of 10 days' duration.

Ten days before admission he had a sudden attack of paroxysmal nocturnal dyspnea and came immediately to the hospital Accident Room. A greatly enlarged heart with murmurs typical of aortic insufficiency were noted, and the patient was started on digitalis. The first day 0.8 Gm. was given, 0.1 Gm. t.i.d. for the next four days, and 0.1 Gm. q.d. thereafter. He felt well until the night before admission when there was another severe attack of paroxysmal nocturnal dyspnea.

On admission the blood pressure was 170/30, and there were peripheral signs of aortic insufficiency including nodding of the head with systole. There was no orthopnea. The heart was enormously enlarged to percussion, and the point of maximum cardiac impulse was 13.5 cm. to the left of the midline in the seventh intercostal space. There were no precordial thrills. The heart sounds were obliterated by murmurs. There was a grade 3 diastolic murmur heard down the left sternal border to the apex, where a late diastolic murmur was heard. A grade 2 systolic murmur was heard at the aortic area. The lungs were clear to percussion and auscultation. The liver was not palpable. There was no peripheral edema.

The serological test for syphilis was positive, and the heart was enlarged by x-ray. There was left axis deviation by electrocardiogram.

Digitalis 0.2 Gm. was given on the first day and 0.1 Gm. daily thereafter. A low salt diet was used. After the first day there was no dyspnea. The patient was discharged asymptomatic on March 13, 1942.

He felt well for several months on this regime, but gradually there was increasing shortness of breath and ankle edema. He arrived at the Accident Room in acute pulmonary edema on July 18, 1942, and died before phlebotomy could be done.

At autopsy the heart weighed 720 Gm.

The right coronary cusp was broken from its attachment to the commissure at its left side for about 6 mm. The edges were healed and rounded (Fig. 2). The commissures were thickened without much separation of the leaflets. The aortic cusps were thickened and rolled at the edges. There was typical syphilitic aortitis. All the heart chambers were dilated and hypertrophied. There was pulmonary edema.

The liver weighed 2200 Gm. and showed chronic passive congestion.

Comment: This patient had rapidly progressive cardiac failure associated with a loud aortic diastolic murmur and peripheral signs of aortic insufficiency.

Case 6: M. G. (J.H.H. History No. 512967), a 37 year old Negress, came to the Johns Hopkins Hospital September 12, 1949, complaining of shortness of breath for one month.

There had been eleven pregnancies in the past, four of which had resulted in miscarriages in the second and third months. The serological test for syphilis had been consistently negative. A heart murmur had never been heard during hospitalization for delivery.

One month prior to admission sudden dyspnea had occurred at night without previous exertion. During the next three weeks there had been rapidly progressive left sided heart failure, and, because of the peculiar heart murmur, admission was advised for further study.

Physical examination revealed a temperature of 100° F., a pulse of 88, respirations 48, and a blood pressure of 110/72. There was orthopnea and Cheyne-Stokes breathing. The teeth were carious. There were signs of a pleural effusion at the right base, and medium moist rales were heard at the left base.

The heart was enlarged to the left with the point of maximum impulse in the sixth intercostal space in the anterior axillary line. There was a systolic thrill to the left of the sternum.

Harsh systolic and diastolic murmurs were heard over the entire precordium, loudest in the second and third interspaces along the left sternal border. The murmurs were discrete and not continuous. The pulse was collapsing in nature. The liver was felt 2 cm. below the right costal margins. There was mild ankle edema. There was no cyanosis.

Laboratory data showed the serological test for syphilis to be negative. Initial erythrocyte and leucocyte counts were normal. Urine showed two plus albuminuria concentrated to 1.016 and the phenolsulfonphthalein test showed 65 per cent elimination of the dye in 2 hours. Twelve blood cultures, one from the pulmonary artery, were sterile.

The left ventricle and left auricle were enlarged on fluoroscopy. There was pulmonary congestion and a right pleural effusion. The electrocardiogram revealed sinus tachycardia and digitalis effect.

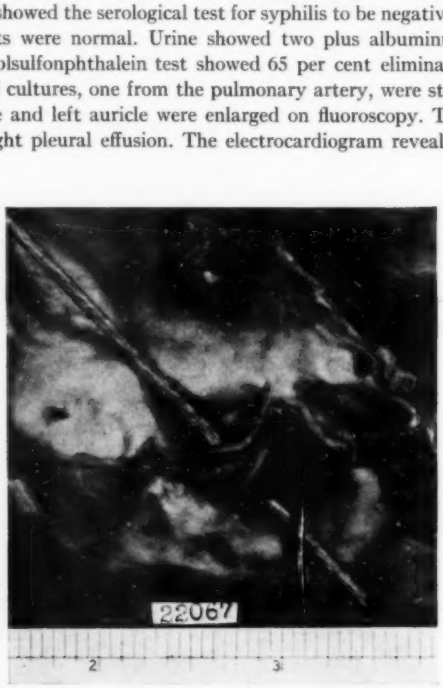

FIG. 3. Aortic valve of Case 6 showing the probe passing from the aorta behind the posterior cusp into the left ventricle.

The patient was placed on bed rest; the salt intake was limited to 2 Gm. daily; full digitalization was accomplished and mercuzanthine was given. The systolic and diastolic murmurs on admission had been distinct, but subsequently they became continuous.

The possibility of a patent ductus arteriosus was considered because of the continuous murmur. Rupture of a sinus of Valsalva into the right ventricle was considered more likely because of the sudden onset of symptoms and the progressive course.

Cardiac catheterization was carried out by Dr. Richard Bing for the purpose of getting a pulmonary blood culture and ruling out patent ductus arteriosus or ruptured sinus of Valsalva. The findings are shown in Chart I and ruled out both of these possibilities.

During the second week the symptoms of cardiac failure progressed. Tachycardia persisted; dyspnea increased; cyanosis appeared.

Despite all therapeutic measures rapid progression of cardiac failure continued until death on October 23, 1949.

The heart weighed 350 Gm. at autopsy. There was dilatation of both the right and left auricles, but hypertrophy was more severe. There was syphilitic aortitis. At the base of the

sinus of Valsalva there was an aneurysm behind the posterior and left coronary cusp (Fig. 3). The base of the posterior cusp was torn loose from its attachment to the aorta so that there was a free communication between the aorta and the left ventricle. The valve margins were normal.

There was pulmonary edema. There were multiple small emboli to both lungs. The liver weighed 1200 Gm. and showed chronic passive congestion.

The pulmonary emboli originated from the tubo-ovarian vessels which were dilated, tortuous and filled with many thrombi. One large thrombus extended in the ovarian vessels to the level of the bifurcation of the aorta.

Comment: The aortic murmur changed in this patient while under observation in the hospital from a to-and-fro murmur to a machinery murmur. This suggests that dissection of the aneurysm was occurring at this time. It is of interest that the patient had a negative serological test for syphilis and never received any antisyphilitic therapy.

CHART I

Results of Cardiac Catheterization on Patient M. G. (Case 6)

CATHETER POSITION	O_2 CONTENT (VOL. %)	PRESSURE (mm. Hg.)
Superior Vena Cava	5.66	
Right Auricle	6.29	19/9
Right Ventricle (apex)	7.23	63/24/16
Right Ventricle (outflow)	7.52	
Main Pulmonary Artery	6.80	56/40
Right Pulmonary Artery	6.73	
Femoral Artery	16.00	
Capacity	17.30	
Saturation	92.40	

Cardiac catheterization was helpful in differentiating a rupture of the sinus of Valsalva into the right heart and a patent ductus from a ruptured or retroverted aortic valve. It revealed the physiological pattern to be expected in severe aortic insufficiency. The high diastolic pressures in the right ventricle and auricle suggested that the right ventricle was also failing.

Case 7: W. R. (J.H.H. History No. 120194), a 49 year old Negro, entered the hospital February 9, 1942, complaining of shortness of breath and a cough.

For about 5 years he had noted some exertional dyspnea. One year before admission, the serological test for syphilis was found to be positive; subsequently, syphilitic aortic insufficiency was diagnosed. Four courses of bismuth and 3 of neoarsphenamine were given. The chest x-ray showed extensive fibrosis of both lung fields.

For the two weeks before admission, the dyspnea grew much worse, ankle edema and orthopnea appeared.

Physical examination showed the blood pressure to be 138/52 with peripheral signs of aortic insufficiency. There was orthopnea and nodding of the head with systole. There were moist rales at the bases posteriorly. There was no precordial thrill. The point of maximum cardiac impulse was 11 cm. to the left of the midsternal line in the fifth intercostal space.

There was a grade 3 high-pitched blowing diastolic murmur heard at the aortic area and along the left sternal border. A grade 2 systolic murmur was heard at the aortic area. The heart sounds were obliterated by the murmurs. The liver edge was felt 5 cm. below the right costal margin. There was moderate sacral and ankle edema.

The blood serological test for syphilis was positive. The heart was enlarged by x-ray.

The patient was fully digitalized, given mercupurine and placed on a low salt diet. There was only slight improvement. Two days after admission a presystolic murmur was heard at the apex for the first time. He became disoriented; there was gradual increase in the dyspnea, and he died on February 28, 1942.

At autopsy the heart weighed 600 Gm. Both ventricles were dilated and hypertrophied. There was syphilitic aortitis as well as arteriosclerosis of the aorta. The commissure between the left coronary and posterior cusp was torn away from the wall of the aorta for a distance of about 1 cm. The two cusps sagged downward and forward. The edges of the ruptured commissure were rounded and smooth.

The liver weighed 1000 Gms.

Comment: The patient received inadequate antisyphilitic treatment, and there was obvious syphilitic aortitis at autopsy. The heart failure progressed very rapidly and death occurred within 5 weeks of the beginning of symptoms. There was little improvement on the usual procedures used in cardiac failure.

Case 8: I. W. (J.H.H. History No. U-9559), a 29 year old Negro, came to the hospital December 24, 1926, complaining of pain in the chest of 4 wee' . duration.

He had a urethral discharge twice at the age of 18 but denied syphilis. At 21 he had generalized joint pains without fever.

The present illness started suddenly one month before admission with dull pain in the left chest worse on breathing. Shortly thereafter a cough productive of a small amount of white sputum developed. Twenty-four hours after the onset of the pain in the chest, dyspnea forced him to take to bed. One week before admission there was slight swelling of the ankles which increased greatly before admission. At this time bright red blood appeared in the sputum.

On physical examination the temperature was 102.6° F., the pulse was 110 and the respirations were 32. The blood pressure was 130/64. He appeared very sick with extreme dyspnea, orthopnea and a racking cough productive of gross red blood. There was periodic breathing, cyanosis and anasarca. There were no petechiae. The rhythm was regular except for occasional premature ventricular beats. The pulse was collapsing in type with a to-and-fro murmur heard over the femoral vessels. The point of maximum impulse could be seen in the midaxillary line in the fifth interspace. A diastolic thrill was felt at the apex and a systolic thrill was felt at the pulmonic area. On auscultation at the apex, the first sound was loud and booming followed by a coarse systolic murmur. The second sound was difficult to distinguish, but a soft late crescendo diastolic murmur could be made out. In the fourth interspace to the left of the sternum another diastolic murmur was heard which was prolonged and rough and increased in intensity up to the second interspace. In this area a short systolic murmur was heard. The second sound was distinctly heard here. A double murmur was heard along the right border of the sternum as far down as the fourth interspace. The aortic second sound was replaced by an early diastolic murmur. A rough to-and-fro friction rub was heard at both bases. The liver edge was felt 8 cm. below the costal margin and was slightly tender. There was moderate ascites. There was massive edema of the ankles.

The red blood count was 3.3 million with a hemoglobin of 71 per cent. The white blood

count was 21,200 with 75 per cent polymorphonuclear leucocytes. The Wassermann test was positive. The blood culture was sterile. The heart was enlarged and the aorta dilated by x-ray with signs of congestive failure in the lung fields. The electrocardiogram showed left axis deviation. The urine contained a trace of albumen throughout hospitalization.

There was a temperature of 104.8° F. on the second day, but thereafter the temperature was normal until 5 days before death when it rose to 102° F. and stayed in this range until death. He was digitalized, given morphine, and the fluid intake was limited.

Opinion was somewhat divided as to the diagnosis. Some thought the bloody sputum might be due to pulmonary tuberculosis with erosion into the vascular system. Others explained the hemoptysis on the basis of pulmonary infarctions. When the Wassermann test returned positive, the possibility of syphilitic aortic insufficiency with an Austin Flint murmur at the apex was advanced, and the pulmonary bleeding was explained as the result of an aneurysm eroding the tracheal vessels. He improved clinically during the first 20 days of hospitalization with lessening of the dyspnea and orthopnea. The friction rub disappeared. The heart became smaller on physical examination. On the 25th hospital day, there was sudden dyspnea with marked cyanosis and a fast thready pulse. The white blood count at this time was 25,200. He continued to cough up almost pure blood. Shortly thereafter he lapsed into coma and died after 24 hours.

At autopsy there was some ankle edema. There was no pleural or abdominal fluid. The heart weighed 680 Gm. The chambers were dilated. There was a thrombus in the right auricular appendage. The valves except the aortic were normal in appearance. The aortic valve was most striking, the cusps being roughened and thickened by a fresh looking, yellow syphilitic process which extended into it from the root of the aorta and the sinuses of Valsalva. The right posterior cusp had broken away from its attachment to the aorta along one side and flapped freely into the ventricle. There were thrombi in the left pulmonary artery, but there was no complete obstruction to the artery. There were hemorrhagic infarcts of the lungs with a confluent lobular pneumonia. The liver weighed 1450 Gm. and the spleen weighed 140 Gm. Both of these organs showed extreme chronic passive congestion. There was syphilitic aortitis both grossly and microscopically.

Comment: The patient died within two months of the onset of symptoms. The pericardial friction rub was not fully explained, but may have been pleuropericardial, secondary to embolism.

ARTERIOSCLEROSIS

Of the 52 cases of rupture of the aortic valve collected and summarized by Phillips, Easton and Fulton (2), 26 had atheromatous aortic valves. In the following case this abnormality was present and probably contributed to weakening of the valve and rupture.

Case 9: J. B. (J.H.H. Autopsy No. 1839), a 49 year old Negro laborer entered the hospital for the second time on December 26, 1901, complaining of shortness of breath since August, 1901. The illness had started in August when he began to have paroxysms of coughing lasting about an hour with exacerbations at night. He had coughed up some blood, mixed with his sputum. There was increasing dyspnea. Swelling of the ankles was first noted four days before his first admission on November 19,1901. There had been 52 pounds weight loss.

On physical examination in November he was large and well nourished. There was slight dyspnea and cyanosis. The pulse was collapsing in type. There were fine rales at the bases

and coarse rhonchi over both lung fields. Breath sounds were obscured by cardiac murmurs. The heart was enlarged 13.5 cm. to the left of the midline in the sixth interpsace. The apical impulse was punctate. There was a diastolic thrill felt over the entire precordium, maximum at the apex and in the third left interspace. A loud diastolic murmur could be heard in the aortic area and in the pulmonic where it was loudest. It could be heard 6 inches from the chest wall with the naked ear. It sounded like the base strings on a cello. A loud presystolic rumble was heard at the apex but there was no definite systolic murmur. The liver was felt 6 cm. below the costal margin. There was marked edema of the legs.

There was no fever. On bed rest alone the general condition improved, and he stopped coughing up blood. The dyspnea disappeared and the ankle edema decreased. He was discharged December 6, 1901.

The patient re-entered the hospital December 26, 1901, complaining of increased shortness of breath. He had felt well for two weeks following discharge, but one week before the second admission shortness of breath returned, and the abdomen and legs became swollen. The cough was productive of a small amount of blood-streaked sputum. There had been marked exertional dyspnea.

On physical examination on December 26, 1901, there was orthopnea and cyanosis. The lungs were resonant throughout. There were mucous rales at the bases, and sonorous and sibilant rales universally. The point of maximum impulse could be seen in the sixth interspace 15.5 cm. to the left of the midsternal line. There was a diastolic thrill felt over the entire heart. A diastolic murmur at the aortic area seemed to start in late systole and continue into diastole. At the apex the first sound was replaced by a systolic murmur which was not transmitted. A loud diastolic murmur was heard over the whole precordium, and also over the vessels of the neck, in the axilla, and over the back. The edge of the liver was easily felt. There was slight edema of the ankles. The patient died suddenly on the second hospital day.

At autopsy there was slight ankle edema. The peritoneal cavity contained a considerable amount of clear fluid. The heart weighed 870 Gm. All chambers were dilated. All valves were normal except the aortic. The valves were thickened and curled at the edges. At the left extremity of the posterior cusp, the valve was torn almost to the base. There was pulmonary edema with chronic passive congestion of the liver and spleen. There was severe arteriosclerosis, but no syphilis on microscopic examination.

Comment: This patient had the loudest murmur heard in this group. It is possible that muscular exertion had some part in the rupture, since he was a farmer doing heavy work. No history of a sudden onset of pain in the chest, however, could be elicited.

Twenty-seven per cent of the autopsied cases of aortic cusp rupture reported by Howard (1) had absolutely normal valves at postmortem examination. In the following case, the valves and aorta appeared normal grossly and microscopically, and the cause of the aortic insufficiency was a perforation rather than a tear. No adequate explanation can be advanced for the perforation. A healed bacterial endocarditis seems possible, but unlikely.

Case 10: L. S. (J.H.H. Autopsy No. 2356), a 41 year old Negro hotel porter, came into the Johns Hopkins Hospital on April 30, 1904, for his 20th hospital admission complaining of shortness of breath of two weeks' duration. The first admission had been in 1901 at the age of 37. At that time there was a history of having had gonorrhea and a chancre, followed

by a skin eruption about twenty years previously. The illness which had caused all the subsequent admission had begun four and one-half months previous to the first admission with a "severe cold." The cold grew steadily worse with productive cough, and shortness of breath. About one week before the first admission, the dyspnea had grown worse and orthopnea had appeared. He had also experienced pain over the precordium for the first time.

On examination at the first admission, he was found to be dyspneic and orthopneic. The vital signs were normal. There was mild periodic breathing. Medium and coarse moist rales were heard over both lung fields. The apex impulse was seen in the fifth interspace 14 cm. from the midline. The right border of cardiac dullness extended 6 cm. to the right of the midline in the fifth intercostal space. There were no thrills. At the aortic area the first sound was followed by a soft systolic murmur. The second sound was replaced by a prolonged loud diastolic murmur transmitted down both sides of the sternum, somewhat louder on the left. At the apex the first sound was distinctly audible and was accompanied by a faint systolic murmur, transmitted into the axilla. The second sound was replaced by a soft, prolonged diastolic murmur. To the left of the lower sternum, there was a soft systolic murmur and a prolonged very loud diastolic murmur. There was a collapsing pulse, and a capillary pulse was visible. The liver was felt 3 cm. below the costal margin.

During the first admission, the patient was digitalized with improvement, and was discharged without edema or dyspnea on the 24th hospital day. The diagnosis was aortic insufficiency and mitral insufficiency.

During the subsequent three years he re-entered the hospital 19 times. He would never stay in bed at home and nearly always re-entered with pulmonary edema and ankle swelling. There was never any fever. Early in 1902 pain developed in the abdomen and chest on exertion, and these attacks finally localized over the precordium. Towards the end of his life these attacks ensued every two or three hours on the slightest exertion. They were relieved by nitroglycerin. The physical findings were always about the same as on the first admission. About one year after the first hospital admission, a presystolic rumble developed in a small area at the apex and was always heard subsequently. The heart did not enlarge to physical examination. The liver was always palpable, and there were rales in the chest. The hospitalizations averaged about one month each during which time cardiac compensation was restored. Death occurred suddenly following a cry at the onset of one of the anginal attacks.

At autopsy there was slight edema of the calves of the legs. The peritoneal cavity contained 300 cc. of fluid. The heart weighed 800 Gm. A lenticular perforation of the posterior cusp of the aortic valve was found. This measured 16 mm. by 18 mm. Mild pulmonary edema was present. The liver weighed 1700 Gm. and the spleen weighed 300 Gm.

Comment: The cause of the perforation of the cusp in this patient is unknown. This patient is the only one in the series who had angina. Despite this evidence of coronary insufficiency, he lived much longer than any of the other patients.

DISCUSSION

Intracardiac rupture include ruptures of chordae tendinae (4), papillary muscles (5), the interventricular septum (6), the sinus of Valsalva (7), and the heart valves. The pathognomonic sign associated with these conditions is the sudden appearance of a loud murmur in a heart previously known to be normal. These lesions are usually associated with trauma, bacterial endocarditis,

syphilis, myocardial infarction, or arteriosclerosis. They must be distinguished clinically from extracardiac ruptures of the aorta into the vena cava, or pulmonary artery as well as from dissecting aneurysms. Very rarely murmurs appear suddenly with pulmonary emboli and with exsanguinating hemorrhages.

In rupture of the aortic valve, there are (in addition to the sudden appearance of the murmur of aortic insufficiency), signs of aortic insufficiency such as Corrigan pulse, Durozier's murmur, pistol shot sounds over the brachial and femoral vessels, a visible capillary pulse, a wide pulse pressure with low or absent diastolic pressures. Occasionally a patient will notice the sudden onset of a murmur in the chest. Sudden severe dyspnea and anginal pain sometimes occur at the time of rupture. In practice, few patients are seen who are without murmurs at one examination and return in a short time with signs of aortic insufficiency. The diagnosis is suggested rather by loud to-and-fro murmurs of aortic insufficiency associated with a short and severe course of cardiac failure which does not respond well to the usual measures of treatment. Even when the classical findings are present, however, rupture of an aortic valve is almost impossible to distinguish from retroversion of an aortic cusp (8) or from rupture of the sinus of Valsalva into the right atrium. The latter condition can be distinguished from aortic cusp rupture by cardiac catheterization with the finding of a relatively high blood oxygen content in the right ventricle or pulmonary artery. Right axis deviation and a continuous murmur are usually present with a ruptured sinus of Valsalva into the right heart.

Transmission of the Aortic Diastolic Murmur

Chart 2 shows the transmission of the diastolic murmur, the duration of life after onset of symptoms of cardiac failure, and the cusp ruptured. The patients with bacterial endocarditis were not included because of the frequency of vegetations on valves other than that ruptured.

Four patients had rupture of the right coronary cusp. Two of these had loud rasping murmurs heard over the entire precordium. Two others had transmission of the diastolic murmur to the apex where the murmur occurred late in diastole, but had no presystolic accentuation.

Belthazar Foster (9) believed that transmission of a high pitched aortic diastolic murmur to the apex was indicative of deformity of the posterior aortic cusp. The murmur he described was a late diminuendo diastolic apical murmur and not the Austin-Flint murmur. The finding of this murmur in two patients with rupture of the right aortic cusps indicates its non-specific origin.

Cole and Cecil (10) in their description of the aortic axillary diastolic murmur mention transmission of an aortic diastolic murmur to the apex and axilla with involvement of the anterior cusps.

The loud rasping murmur heard in two of the cases has been called the bruit

de scie and may be characteristic of ruptures of the right coronary cusp (11). Nevertheless, in case 8 with a posterior cusp ruptured, a very loud murmur described as "Cello String" was heard.

One patient had a perforated syphilitic aneurysm at the base of the posterior cusp. Here the murmur was at first to-and-fro with transmission of the diastolic murmur down the left sternal border. Later the murmur became continuous with the same transmission.

One patient had rupture of the commissure between the left coronary and posterior cusp. In this patient an Austin Flint murmur was heard at the apex.

Three patients had ruptures or perforations of the posterior cusp alone. All of these patients had Austin Flint murmurs. In this series then, an Austin Flint

CHART II

Findings in Nine Case of Rupture of the Aortic Valve

	SURVIVAL TIME FROM ONSET OF SYMPTOMS	CHARACTER OF DIASTOLIC MURMUR	DIASTOLIC MURMUR DURATION	DIASTOLIC MURMUR TRANSMISSION	CUSPS RUPTURED
J. S. Case 2	8 months	Grade 4, rasping	First ⅔ of diastole	Over entire precordium	Right coronary
E. N. Case 3	6 weeks	Grade 4, rasping	First ⅔ of diastole	Over entire precordium	Right coronary rupt. and perf.
L. A. Case 4	6 weeks	Grade 4, loudest at apex	First ½ of diastole	Apex. No Austin Flint	Right coronary
A. W. Case 5	5 months	Grade 3	First ½ of diastole	Apex. Late diastolic. No Austin Flint*	Right coronary
M. G. Case 6	10 weeks	Grade 3 continuous	All of diasole	Left sternal border	Posterior cusp aneuryam
W. R. Case 7	1 month	Grade 3	First ½ of diastole*	Apex* Austin Flint	Posterior cusp Left coronary commissure
I. W. Case 8	2 months	Grade 4	First ½ of diastole	Apex Austin Flint	Posterior cusp
J. R. Case 10	5 months	Grade 5 Cello String	First ½ of diastole	Apex Austin Flint	Posterior cusp
L. S. Case 11	3 years	Grade 3	First ⅓ of diastole	Over entire precordium Austin Flint	Posterior cusp perforated

* Stethogram

murmur was present only when the posterior cusp was involved. Herrmann (12) reported the presence of an Austin Flint murmur in lesions of the posterior aortic cusp.

This finding supports the theory that the Austin Flint murmur originates from deflection of the aortic leaflet of the mitral valve into the mitral opening due to the regurgitating blood stream from the aorta. Injury of the posterior aortic cusp would allow the blood stream to impinge on the mitral aortic leaflet, whereas injury of the left or right coronary cusps would deflect the regurgitating blood toward the ventricular wall.

There was no confirmation of Foster's suggestion that ruptures of the posterior cusp had a better prognosis than ruptures of the left or right coronary cusps. The prognosis was uniformly bad, eight months being the longest survival time after the onset of symptoms of cardiac failure except in the patient

with a perforation of the posterior cusp. True angina pectoris occurred in this same patient.

It has been suggested that the duration of the aortic diastolic murmur gives a rough indication of the degree of insufficiency, a short diastolic murmur indicating a large amount of regurgitation, and a long diastolic murmur suggesting little regurgitation. In this series the duration of the diastolic murmur was not correlated with the degree of regurgitation as judged from autopsy.

Once heart failure had occurred, there was little response to the usual measures of treatment. Thus prevention and adequate treatment of the underlying cause of the rupture, such as syphilis and bacterial endocarditis must be hoped for in the future. Early treatment of streptococcal tonsillitis and nasopharyngitis with penicillin may cut down the incidence of rheumatic fever from this cause (13). Bacterial endocarditis must be suspected early in any patient with a murmur and persistent fever. Careful bacteriological study, early and prolonged treatment with the indicated antibiotic should decrease the incidence of valvular ruptures (14). If rupture occurs prior to treatment, antibiotics may still cure the infection, but the patient will die of heart failure.

Two of the seven patients with proved syphilis at autopsy had negative Wassermann reactions. The need for a more reliable test for syphilis is well known (15). Two other patients gave a history suggestive of syphilis, and one had not completed a course of arsphenamine and bismuth 22 years before the rupture.

There is reason for hope, therefore, that early treatment of rheumatic fever, bacterial endocarditis and syphilis may help prevent ruptures of valves secondary to these diseases.

Summary

Twenty-four proved cases of non-traumatic aortic valve rupture are reported. Fifteen were due to bacterial endocarditis, seven to syphilis, one to arteriosclerosis, and one was idiopathic. Sudden chest pain and an audible murmur may accompany the rupture, but in this series, the diagnosis was most frequently suggested when aortic insufficiency was associated with rapid and intractable heart failure, in the presence of bacterial endocarditis or syphilis.

Analysis of the murmurs produced suggests that the Austin Flint murmur is usually associated with injury to the posterior cusp, whereas injury of the anterior cusps may give an aortic axillary diastolic (Cole-Cecil) murmur, the bruit de scie (Hodgkin-Key) with transmission of the murmur to the right of the lower sternum (Belthazar Foster).

One case with a ruptured syphilitic aneurysm through the posterior coronary cusp first had a to-and-fro murmur and later a continuous murmur. Differentiation of ruptured aortic valve from a rupture of the sinus of Valsalva into

the right heart and from a patent ductus arteriosus was accomplished by cardiac catheterization.

Since little can be done for these patients once a rupture of the aortic valve has occurred, emphasis must be placed on prevention of rheumatic and syphilitic heart disease and early and prolonged therapy for bacterial endocarditis.

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HEPATITIS IN MICE, OF PRESUMED VIRAL ORIGIN*

(A Preliminary Report)

JANET JORDAN, AND GEORGE S. MIRICK

Department of Medicine, The Johns Hopkins University School of Medicine

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The viral etiology of human hepatitis has been established by experiments with volunteers. For about 20 years many workers have attempted to transmit this infection to laboratory animals. Negative results using many strains of virus and many species of animals have been summarized (1, 2, 3).

There is evidence which suggests that the severity of hepatitis is influenced by the environment of the host (4) and may be enhanced by some toxic substances (5–8). Moreover, it has been shown that cortisone (9–12) and urethane (13) may increase the severity of some other virus infections. It was decided to use adjuvants in an attempt to adapt the virus of human hepatitis to Swiss albino mice.

EXPERIMENTAL

Two sources of virus were tested. One was pooled serum taken during the incubation period from patients who subsequently developed homologous serum jaundice; the other was a 10% saline extract of the liver of a patient (C. B.) who died with acute liver atrophy 5 days after developing the first symptoms of hepatitis. Neither source has been checked for human infectivity. These materials were inoculated intraperitoneally (0.5 cc./mouse) into groups of mice which were given either of two adjuvants, the hepatotoxic alkaloid monocrotaline (5, 14) or urethane. Mice were sacrificed at weekly, semimonthly and monthly intervals and 0.3 cc./mouse of a 10% saline extract of the pooled livers, spleens, and kidneys was passed serially in other mice which were given the adjuvants. Uninfected controls both with and without the adjuvants were treated in a similar fashion. The monocrotaline was administered in a buffered solution, 0.2 mg./gm., intraperitoneally one week before or simultaneously with virus inoculation. Urethane was given as a 0.1% solution to drink throughout the entire experimental period.

One mouse in the fourth serial monthly passage in the group inoculated originally with the patient's liver and receiving urethane, developed serous ascites and hepatosplenomegaly approximately 4 weeks after injection. Microscopic sections of the liver showed mononuclear infiltration around the portal and central veins, in the subcapuslar area and in small scattered foci. No

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similar disease occurred in the other inoculated or control groups after 8 passages.

An extract of pooled liver, spleen, and kidney from the sick mouse was injected into other mice and has resulted in a similar disease at 3–4 weeks in five subsequent serial passages in both normal mice and those receiving urethane. In the later passages gross lesions were more pronounced, with red mottling of the enlarged livers and occasional jaundice. Microscopic sections showed marked infiltration and diffuse areas of parenchymal liver necrosis as shown in Figs. 1 and 2.

The isolation of this agent from the liver of C. B. was attempted a second time by the same method. The mice remained well for three passages at monthly intervals but on the fourth passage the disease appeared, this time both in mice receiving urethane and those given water to drink.

Obvious disease has developed in about $\frac{1}{3}$ of all mice inoculated with passage material thought to be infectious. In positive individual experiments all mice became sick but negative experiments have occurred unpredictably and for reasons as yet unknown. The positive experiments permit certain conclusions. The disease is rarely fatal ($\pm 2\%$). The incubation period is 3–4 weeks. Mice one, two and five months of age and of three different strains are susceptible. Saline extracts of the liver or spleen in a final concentration of 1:1000, ascitic fluid and blood from sick mice have all been infectious. Mice have been infected by the intraperitoneal and intravenous routes but did not become sick when inoculated intranasally or when fed infectious material. Intracerebral inoculation has resulted in liver disease but not meningitis. The agent remains infectious for at least three hours at room temperature, 72 hours at 4°C. and three months at -70°C. but has failed to infect when heated at 56°C. or over for one hour. Rabbits, guinea pigs, hamsters and chick embryos, inoculated with material infectious for mice, have remained well and organ extracts from these hosts have failed to infect mice.

Repeated cultures have not yielded any pathogenic bacteria but the infectious extracts have not yet been successfully filtered. Giemsa stained preparations did not show inclusion bodies and darkfield examination revealed no leptospira. The agent is thought to be a virus but does not have the characteristics of those known to be commonly carried by mice. It differs from the virus of lymphocytic choriomeningitis (LCM) in not producing meningitis when inoculated intracerebrally into LCM-susceptible mice. It did not grow in the chick embryo or infect guinea pigs. Moreover, mice convalescent from hepatitis were susceptible to LCM virus. An agent of the psittacoid group seems to be excluded by the absence of intracellular inclusions in Giemsa stained preparations. Moreover, the serum of rabbits intensively immunized with organ extracts from infected mice did not fix complement with Lygranum

antigen. The extensive infiltration of the liver has suggested leukemia but this disease is unlikely because of normal leucocyte counts and the survival of most infected mice. The possible relationship of this disease to infectious hepatitis in humans is discussed below.

DISCUSSION

A few workers have reported liver disease in birds or mammals inoculated with or fed material thought to contain human hepatitis virus. Liver lesions developed in canaries (15, 16), pigeons, ducklings, and starlings (17), swine (18, 19), horses (20), rats (21), guinea pigs (22), a ferret (23), a rabbit (24), and a monkey (8). Stokes et al. (25, 26) have passed hepatitis virus through chick embryo tissue culture and by serial intra-amniotic inoculations of chick embryos. The majority of the embryos remained healthy but an agent was recovered from them which induced a mild non-icteric illness in volunteers. Amniotic fluid gave a positive skin test in 40% of controls and 100% of patients convalescent from epidemic hepatitis (27).

Other workers have had difficulty in duplicating some of the experiments described. Moreover, it has become apparent that many animal species carry latent viruses that may cause forms of hepatitis which appear to be distinct from the human disease. A transmissible form of hepatitis has been shown to occur naturally in birds (17), horses (28, 29, 30), swine (18), and dogs (31, 32). Mice infected with some strains of LCM virus develop liver lesions and ascites (33). Olitsky and Casals (34) have described cellular necrosis, intranuclear inclusion bodies and infiltration in the livers of normal stock albino mice. These lesions increased with age and were non-transmissible. Recently, Gledhill and Andrewes (35) have described a virus causing transmissible hepatitis in mice.

In attempts to adapt human hepatitis virus to a laboratory animal each positive result must be considered in the light of possible infection with a latent agent carried by the experimental host. Investigations are now in progress to determine the possible relationship of the disease in mice described in this paper to epidemic hepatitis in man.

SUMMARY

An agent causing transmissible hepatitis in mice has been isolated. Its possible relationship to the virus of human hepatitis is discussed.

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FIG. 1. Photomicrograph (× 150) of the liver of a mouse sacrificed 32 days after infection in the 7th passage. No urethane was given. Note diffuse infiltration particularly in the subcapsular area, occasional giant cells, dilatation of the sinusoids and disorganization of the hepatic architecture.

FIG. 2. Photomicrograph (× 150) of the liver of a mouse sacrificed 27 days after infection in the 8th passage. No urethane was given. Note diffuse infiltration and patchy areas of necrosis.

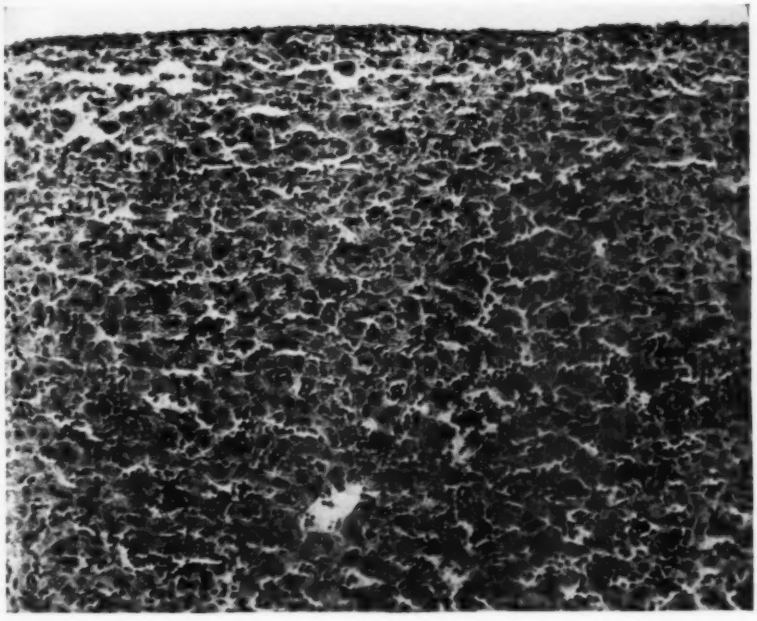


FIG. 1

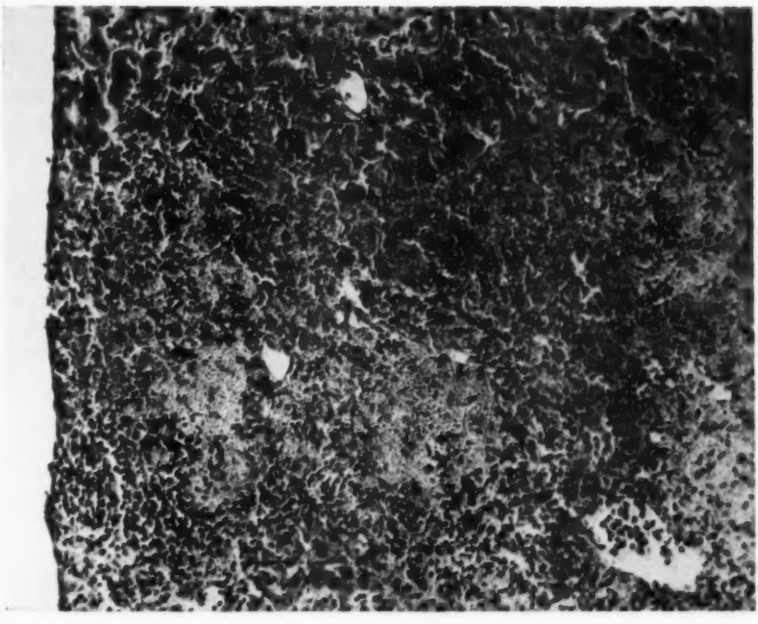
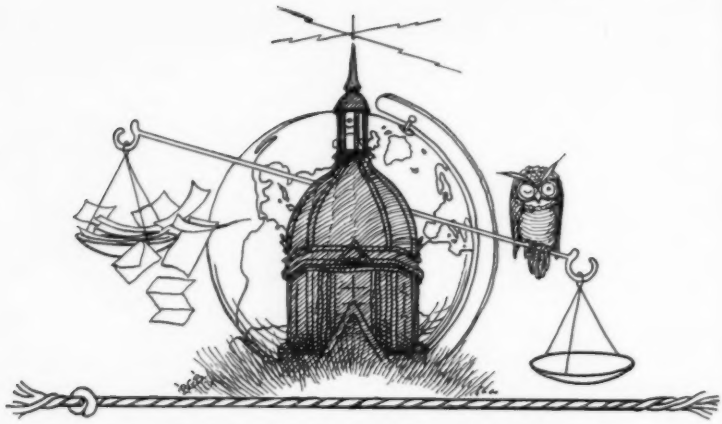


FIG. 2



BOOK REVIEWS

(These reviews represent the individual opinions of the reviewers and not necessarily those of the members of the Editorial Board of the Bulletin)

Physiology of Shock. By CARL J. WIGGERS. 459 pp., $5.00. *The Commonwealth Fund, New York.*

The author of this monograph, an eminent physiologist, has probably been interested in experimental shock for a longer time than anyone who is still actively engaged in working on it. He is thoroughly familiar with the literature in this field, he is an expert on the measurement of various circulatory dynamics, and he has developed a very good method for producing irreversible post-hemorrhagic shock. The significant findings are that the late stages of shock are accompanied by capillary pooling and myocardial depression. Metabolic changes which have been investigated so extensively recently are said to be the result rather than the cause of progressive circulatory failure.

The method used in the author's studies may be criticized on the ground that irreversibility or an antemortem state is being studied. Even though the value of this monograph would be enhanced by a detailed consideration of some of the earlier alterations in shock, it is an important book and should be of value to everyone working in this field.

ALFRED BLALOCK

A Textbook of Pathology, 2nd edition. By ROBERT ALLAN MOORE. 1048 pp., $12.50. *W. B. Saunders Co., Philadelphia, Pa.*

Dr. Moore has extensively revised, rewritten and brought up to date his textbook of pathology, the first edition of which was published in 1944. This book, in this reviewer's opinion, is the best one available today for medical students. This is so, if for no other reason than because it is written entirely by one man and the confusion, overlapping, and lack of integration that are so rampant in the multiple-author texts are avoided. The general plan of the first edition is retained including the paragraphs captioned, "Clinico-Pathologic Correlation," and "Physiologic Considerations." Even though one gets the distinct impression the author is more at home with discussions of the pathology side of the picture this is a desirable addition to a student's textbook. Actually the plan used in texts in internal medicine which have paragraphs headed, Morbid Anatomy, is used in reverse.

The chapters on infectious diseases are very good, including lucid chapters on virus diseases. One might wish the discussions of vascular diseases were as good. Photographs and illustrations are numerous and, generally speaking, much above average. The references are excellent and up to date, including lists of the major journals which deal with the subject under discussion.

However teachers in pathology are still awaiting a modern text offering the really desired illustrations and descriptions of disease integrating the pathology, functional disturbance, and clinical aspects, all of which are part of the disease.

S. L. E.

Diseases in Old Age. By ROBERT T. MONROE. 407 pp., $5.00. Harvard University Monographs in Medicine and Public Health, 11. *Harvard University Press, Cambridge, Mass.*

Dr. Monroe, head of the Geriatric Clinic of the Peter Bent Brigham Hospital, has surveyed the records of 7941 individuals over 61 years of age seen on the medical service of that hospital during the period 1913 to 1943, the first 30 years of its existence. A reviewer of clinical records is at the mercy of those who originally observed the patient, for there are fashions in diagnosis, bias in anamnesis, and subjectivity in elicitation of physical signs. Aware of this, Dr. Monroe occasionally distrusts his compilations and turns to his own clinical impressions. For example, although hospital records reported marked carotid-sinus irritability only 50 times, he states his conviction that the sinus is overactive in every old person at times. Such statements, provocative but unsupported by convincing evidence, add vitality to this massive accumulation of valuable data.

Although this work is primarily a tally of the incidence of disease in older patients, certain phenomena, long suspected, are verified. It is usual for older patients to have several diseases, so that one is apt to go wrong by insisting on a unitary explanation of symptoms in this age group. Disease itself is modified by age. Older patients, for example, tend to react with less pain and fever. Their angina pectoris is less apt to be agonizing; the pain of myocardial infarction is more apt to be atypical or absent; the acute abdomen may be masked by deceptively slight response.

Throughout the book Dr. Monroe is revealed as a sympathetic physician, appreciative especially of the emotional problems of older patients. Neither patronizing nor insensitive, he strikes a commonsense balance. Not everyone, however, will accept his sweeping disposition of most cases of hypertension as due to emotional influences, although these influences cannot be denied.

This is an informative book. It was worth assembling and, because Dr. Monroe has injected himself into it, a large proportion of it is graceful reading. It is a mistake to consider it a fundamental contribution, however, and the publishers do it a disservice by their jacket blurb offering it as contributing "an entirely new light on heretofore-accepted theories."

K. L. Z.

Pharmacological Basis of Penicillin Therapy. By KARL H. BEYER. 214 pp., $4.50. *Charles C Thomas, Springfield, Ill.*

This monograph on penicillin therapy succeeds rather well in translating basic knowledge of penicillin pharmacology into useful therapeutic precept. The information is up-to-date, errors are few, and the general conclusions reasonable. As the title indicates, only the pharmacology of penicillin therapy is considered, and there is no mention of the bacteriological implications of chemotherapy.

There are two minor defects in the presentation which require exposition. In the first

place basic knowledge of penicillin pharmacology really is not very secure, because of the lack of a chemical method for determining penicillin in biological fluids. The various bacteriological assays, while generally valid, have considerable variation. For example, the author on page 31 states that the volume of distribution of penicillin G is 57 per cent, while others have found it to be 20 per cent. This difference of 300 per cent is almost certainly due to variability in bacteriological assay methods, and provides an estimate of their accuracy. The author has failed to emphasize this low precision and non-specificity of the methodology of penicillin determinations. Secondly, the last 100 pages of the book (47 per cent) are given over to the renal excretion of penicillin. It constitutes a fine discussion of this field but is a little too much for good balance.

The monograph is well printed and the bibliographies are excellent. It can be recommended as the best concise discussion of the pharmacology of penicillin therapy.

C. G. Z.

Pharmacognosy. The Study of Natural Drug Substances and Certain Allied Products. By Robertson Pratt and Heber W. Youngken, Jr. 644 pp., $8.50. *J. B. Lippincott Co., Philadelphia, Pa.*

This book presents the basic principles important to an understanding of pharmacognosy. The organization of the book is such that it can be used for courses in didactic instruction alone, or for courses including both didactic and laboratory work.

The book is divided into six parts covering such things as definitions and sources of drug materials, cellular chemistry, biosynthetic products, practices in procedures, and problems in public health involved in pest and weed control. Each section includes a well selected bibliography.

The entire emphasis is on the integration and application of chemical and physiological principles. This approach to the subject matter makes for a pharmacognosy of practical value to the student and graduate pharmacist. It is a long awaited textbook.

L. K.

Nerve Impulse. Transactions of the First Conference, March 2–3, 1950. Edited by David Nachmansohn. 159 pp., $3.00. *Josiah Macy, Jr. Foundation, New York.*

This interesting book had its origin in stenographic notes of a round-table discussion conducted by the Josiah Macy, Jr. Foundation. Although the participants were allowed to edit their remarks before publication, the informal flavor of the conference has been retained. Your reviewer's first impression was of neurobiology "with its hair down," for questions were frequently more penetrating and persistent and the answers more candid than those likely to occur under more formal circumstances. In general, those who were asked to lead the discussions presented the limitations of their techniques at least as carefully as they did the potentialities.

This book should make easy and informative reading for those who have at least a textbook knowledge of the topics covered. Your reviewer is particularly recommending it to his advanced graduate students. Round table discussions such as this obviously do not yield orderly presentations suitable for introduction to an unfamiliar subject.

The topics treated and the principal discussors are as follows: Potentialities and Limitations of Electrophysiology, Harry Grundfest; Limitations and Potentialities of the Biochemical Approach to Problems of Nerve Conduction, J. H. Quastel; Contributions of Comparative Physiology, C. Ladd Prosser; Potentialities and Limitations of Histological Studies, David Bodian; Ion Exchange and Permeability, Henry B. Steinbach.

Other participants are Frank Brink, Howard J. Curtis, H. K. Hartline, Hudson Hoag-

land, Francis O. Schmitt, George Wald, Frank Fremont-Smith, and H. Houston Merritt, Chairman.

This reviewer looks forward with pleasant anticipation to the report of the second conference in this series, held in 1951, which the sponsors hope to publish more promptly than the first.

M. G. L.

Spatial Vector Electrocardiography. Clinical Electrocardiographic Interpretation. By ROBERT P. GRANT and E. HARVEY ESTES, JR. 149 pp., $4.50. *The Blakiston Co., Philadelphia., Pa.*

Originally printed privately in 1949 for students and staff at Emory University Medical School, this is the first monograph to appear in English on clinical EKG interpretation by vector methods. The method itself is not new, and is the basis for the familiar calculation of "axis deviation" from the standard Einthoven leads. Its application to precordial leads has generally been overlooked in this country because of widespread acceptance of the theory that unipolar leads are local or "semi-direct" leads. Grant and Estes propose that with rare exceptions any lead taken from the body surface reflects the electrical activity of the whole heart, and that each lead represents a different "point-of-view" of a single phenomenon. From inspection of the electrocardiogram, using both extremity and precordial leads, they reconstruct the spatial QRS and T "loops," which represent the electrical forces produced by the heart as a series of vectors having magnitude and spatial orientation with respect to the body. They have applied this theory to the routine interpretation of electrocardiograms from more than 3000 patients.

This volume does not attempt to add another textbook of electrocardiography to the plethora already available, but rather to outline for clinical use a relatively simple and consistent theory of EKG interpretation. Only the QRS and T deflections are considered, and a knowledge of EKG terminology and technique is assumed. Discussion of the mathematical and physical principles concerned has been omitted.

Dogmatism and some inaccuracies inevitably result when such a complex and controversial subject is presented in simplified form, as the authors point out. The specialist will deplore certain oversimplifications, while the student, or the clinician who has only recently memorized the theory of unipolar "ventricular patterns," will feel that the presentation could be simplified further. Some of the generalizations are likely to mislead the reader in his first attempts to apply this theory; for example, the statement that all body-surface leads "can be predicted down to the minutest detail" from the spatial QRS and T loops is not always true for loops derived from routine EKG leads.

Equally open to criticism is the implication that vector direction is more important than magnitude in interpretation, since the spatial direction depends on the relative magnitude in different planes.

Not the least important achievement of this work is the demonstration that currently accepted principles of the interpretation of unipolar leads are still subject to change without notice. It is recommended to anyone interested in the theory or practice of electrocardiography.

W. R. M.

Manual of Massage and Movements, 3rd edition. By EDITH M. PROSSER. 388 pp., $5.00. *J. B. Lippincott Co., Philadelphia, Pa.*

This is an authoritative presentation of British concepts of the role of two modalities in physical therapy. The dominant tendency in the United States, however, is contrary to

much of the theory and application of massage as presented in this text. For example, percussion, vibration and shaking movements are no longer taught or used here, and general massage is employed less and less. In general, contraindications to various types of massage are insufficiently presented and some of the claims of physiological benefits attributable to massage are not supported convincingly.

The larger section on exercise is well arranged, excellently illustrated, and presented in massive detail. Omissions are due perhaps to a difference in opinion concerning rationale of treatment.

M. E. M.

Cybernetics. Transactions of the Seventh Conference, March 23–24, 1950. Edited by HEINZ VON FOERSTER. 251 pp., $3.50. *Josiah Macy, Jr. Foundation, New York.*

These proceedings of the seventh Josiah Macy Conference on Cybernetics show a remarkable change in trend from the preceding ones. For the first time, there is only one paper on purely mathematical notions of neurophysiological functioning of the central nervous system, and an abundance of papers and discussion on higher levels of functioning specifically language, semantics and word meanings. These are, of course, considered from the neurophysiological point of view as well as from those points of view from the other members of the panel, and for the first time, there has been very little resistance on the part of the neurophysiologists in the group to accept a presentation of psychoanalytic concepts involving unconscious motivation and meaning.

The development of language is carried from the engineering point of view which was presented by J. C. R. Licklider in a paper called, "The manner in which, and the extent to which speech can be distorted and remain intelligible," to the development of language in early childhood by John Stroud, with an interpolated paper by Margaret Meade on the anthropologists' experience in learning primitive languages through the use of learning high-leveled linguistic abstractions. The conference was closed with a paper by Lawrence S. Kubie on the relationship of symbolic function in language formation and in neurosis. The discussion of each of these papers was by far the most interesting and illuminating part which is, of course, the purpose of the Josiah Macy Foundation conferences, to bring the various disciplines together for collaboration and mutual enlightenment. With the summing up after the last paper by Dr. Kubie, there was a quite evident change in the attitudes of all concerned in their ability to accept symbolics, that is unconscious symbolic phenomena in the understanding of human behavior of all kinds and including language.

A. McC.

BOOKS RECEIVED FOR REVIEW

Arzneitherapie der Herzkrankheiten. By HANS-JÜRGEN OETTEL. 256 pp. Ganzleinen DM 27. Georg Thieme Verlag, Stuttgart, Germany.

An Atlas of Anatomy, 3rd edition. By J. C. BIOLEAU GRANT. 536 pp., $12.00. The Williams & Wilkins Co., Baltimore, Md.

Atlas der Pathologischen Anatomie. By R. RÖSSLE AND K. APITZ. 298 pp., Ganzleinen DM 87. Georg Thieme Verlag, Stuttgart, Germany.

Clinical Pediatric Urology. By MEREDITH CAMPBELL. 1113 pp., $18.00. W. B. Saunders Co. Philadelphia, Pa.

Das Verstehen und Begreifen in der Psychiatrie. By F. A. KEHRER. 58 pp., Kartoniert DM 5.70. Georg Thieme Verlag, Stuttgart, Germany.

Lane Medical Lectures. Companionship of Water and Electrolytes in the Organization of Body Fluids. By JAMES L. GAMBLE. 90 pp., $2.50. Stanford University Press, Stanford, California.

Medicinal Chemistry. Vol. 1. Edited by C. M. SUTER. 473 pp., $10.00. John Wiley & Sons, Inc., New York.

The Pharmacologic Principles of Medical Practice, 2nd edition. By JOHN C. KRANTZ, JR., AND C. JELLEFF CARR. 1116 pp., $10.00. The Williams & Wilkins Co. Baltimore, Md.

Practical Clinical Psychiatry, 7th edition. By EDWARD A. STRECKER, FRANKLIN G. EBAUGH, AND JACK R. EWALT. 506 pp., $7.00. The Blakiston Co., Philadelphia, Pa.

Praktischer Leitfaden der Beruflichen Hautkrankheiten. By C. CARRIE. 183 pp., Ganzleinen DM 22. Georg Thieme Verlag, Stuttgart, Germany.